

(19)



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(11)

EP 1 284 298 A2

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
19.02.2003 Bulletin 2003/08

(51) Int Cl.7: **C12Q 1/68, A01K 67/027**

(21) Application number: **02255229.3**

(22) Date of filing: **26.07.2002**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
IE IT LI LU MC NL PT SE SK TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **27.07.2001 GB 0118354
07.02.2002 GB 0202883**

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(54) **Identification and use of molecules implicated in pain**

(57) The invention relates to the use of:

- (a) an isolated gene sequence that is down-regulated in the spinal cord of a mammal in response to mechanistically distinct first and second models of neuropathic or central sensitization pain;
- (b) an isolated gene sequence comprising a nucleic acid sequence of any of Tables I to VI;
- (c) an isolated gene sequence having at least 80% sequence identity with a nucleic acid sequence of any of Tables I to VI;
- (d) an isolated nucleic acid sequence that is hybridizable to any of the gene sequences according to (a), (b) or (c) under stringent hybridisation conditions;
- (e) a recombinant vector comprising a gene sequence or nucleic acid sequence according to any one of (a) to (d);
- (f) a host cell containing the vector according to (e);
- (g) a non-human animal having in its genome an introduced gene sequence or nucleic acid sequence or a removed or down-regulated gene sequence or nucleic acid sequence according to any one of (a) to (d);
- (h) an isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence ac-

cording to any one of (a) to (d), or a variant polypeptide thereof with sequential amino acid deletions from the C terminus and/or the N-terminus;
(i) an isolated polypeptide encoded by a nucleotide sequence according to any one of (a) to (d); or
(j) an isolated antibody that binds specifically to a polypeptide according to (h) or (i);

in the screening of compounds for the treatment of pain, or for the diagnosis of pain.

The invention also relates to the use of naturally occurring compounds such as peptide ligands of the expression products of the above gene sequences and their associated signal transduction pathways for use in the treatment of pain.

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Description**FIELD OF THE INVENTION**

[0001] The present invention relates to nucleic acids, their expression products and pathways involved in pain, and their use in screening for molecules that can alleviate pain. The invention further relates to methods for the assay and diagnosis of pain in patients.

BACKGROUND TO THE INVENTION

[0002] Pain is currently classified into four general types. Post-operative acute pain can be successfully treated with existing pain medications of e.g. the opioid and non-steroidal anti-inflammatory (NSAID) types, and is usually short-term and self-limiting. A second type of pain, present e.g. in cancer and arthritis, is also responsive to medication initially with a NSAID and in its later stages with opioids. Neuropathic pain arises from damage to the central or peripheral nerve systems, and is more effectively treated with antidepressants or anticonvulsants. A fourth type of pain called central sensitization results from changes in the central nervous system as a result of chronic pain, these changes often being irreversible and difficult to treat. Nerve pain from shingles or diabetes falls into this and the neuropathic category. Changes occur where pain is at first poorly controlled and gradually progress to the point where a person is sensitive to stimuli which would not normally cause pain, for example a light touch. People with pain of this kind often describe a widening of the pain area to include areas which had originally not been injured or which were thought not to be involved in pain. This classification is, however based on clinical symptoms rather than on the underlying pain mechanisms.

[0003] Opiates such as morphine belong to a traditional class of pain-relieving compounds that are now recognized as binding to opiate receptors. Naturally occurring polypeptides have also been found to have opiate-like effects on the central nervous system, and these include β -endorphin, met-enkephalin and leu-enkephalin.

[0004] Salicin was isolated at the beginning of the 19th century, and from that discovery a number of NSAIDs such as aspirin, paracetamol, ibuprofen, flurbiprofen and naproxen were developed. NSAIDs are by far the most widely used pain-relieving compounds, but can exhibit side effects, in particular irritation of the GI tract that can lead to the formation of ulcers, gastrointestinal bleeding and anemia.

[0005] Interest in the neurobiology of pain is developing: see a colloquium sponsored by the US National Academy of Sciences in December 1998 concerning the neurobiology of pain and reviewed in *The Scientist* **13**[1], 12, 1999. Many pain mechanisms were discussed including the role of the capsaicin receptors in pain, (M.J. Caterina *et al.*, *Nature*, **389**, 816-824, 1997). Large dosages of capsaicin were reported to disable that receptor, (W.R. Robbins *et al.*, *Anesthesia and Analgesia*, **86**, 579-583, 1998). Additionally, a tetrodotoxin-resistant sodium channel found in small diameter pain-sensing neurons (PN3) was discussed (A.N. Akopian *et al.*, *Nature*, **379**, 257-262, 1986) and L. Sangeswaran *et al.*, *Journal of Biological Chemistry*, **271**, 953-956, 1996). Its involvement in transmission and sensitization to pain signals has been reported, (S.D. Novakovic *et al.*, *Journal of Neuroscience*, **18**, 2174-2187, 1998). A further tetrodotoxin-resistant sodium channel has been reported (S. Tate *et al.*, *Nature Neuroscience*, **1**, 653-655 1998).

[0006] Second messenger systems have also been shown to be important since knockout-mice lacking protein kinase C (PKC) γ were reported to respond to acute pain e.g. from a hot surface, but not to respond to neuropathic pain when their spinal nerves are injured (Malmberg *et al.*, *Science*, **278**, 279-283 (1997).

[0007] Present methods for identifying novel compounds that relieve pain of one or more of the types indicated above suffer from the defect that they are dependent either on the relatively limited number of receptors known to be involved in pain or on the empirical identification of new receptors which is an uncertain process. In relation to known receptors, for example the opioid receptor, research directed to improved compounds offers the possibility of screening compounds that have a better therapeutic ratio and fewer side effects. This does not lead naturally to compounds for different pain receptors that have new modes of action and new and qualitatively different benefits. Even when newly identified additional receptors are taken into account, known receptors revolve around tens of gene products. However, there are between 30,000 and 40,000 genes in the genome of an animal and more of them are concerned with nervous system function than with peripheral function. We therefore concluded that a large number of receptors and pathways are important to the transduction of pain, but up to now have remained unknown.

SUMMARY OF THE INVENTION

[0008] It is an object of the invention to provide sequences of genetic material for which no role in pain has previously been disclosed, and which are useful, for example, in:

- identifying metabolic pathways for the transduction of pain

- identifying from said metabolic pathways compounds having utility in the diagnosis or treatment of pain
 - producing proteins and polypeptides with a role in the transduction of pain;
 - producing genetically modified non-human animals that are useful in the screening of compounds having utility in the treatment or diagnosis of pain.
- Identifying ligand molecules for receptors involved in said metabolic pathways and having utility in the treatment of pain.

[0009] It is yet a further object of the invention to provide research tools, for example non-human animals and microorganisms, that can be used in screening compounds for pharmacological activity, especially pain-reducing activity.

[0010] The present invention is based on sequences that are down-regulated in two models of chronic pain, namely streptozocin-induced diabetes and chronic constrictive injury (CCI) to a nerve leading to the spine, for example the sciatic nerve.

[0011] In one aspect, the invention relates to the use in the screening of compounds that are effective in the treatment of pain, or in the diagnosis of pain, of:

(a) an isolated gene sequence that is down regulated in the spinal cord of a mammal in response to first and second models of pain, for example in response to streptozocin-induced diabetes and in response to a chronic constrictive injury to a nerve leading into the spine;

(b) an isolated gene sequence having at least 80% sequence identity with any of the nucleic acid sequences of Tables I - VI, preferably 85% sequence identity, more preferably 90%, increasingly preferably 95%, most preferably 99%;

(c) an isolated nucleic acid sequence comprising a sequence that is hybridizable to any of the gene sequences according to (a) or (b) under stringent hybridisation conditions;

(d) a recombinant vector comprising any of the gene sequences according to (a) to (c);

(e) a host cell containing the vector according to (d);

(f) a non-human animal, for use in the screening of compounds that are effective in the treatment of pain, or in the diagnosis of pain, having in its genome an introduced gene sequence or a removed or down-regulated nucleotide sequence, said sequence becoming down-regulated in the spinal cord of a mammal in response to first and second models of pain, particularly neuropathic or sensitisation pain, for example in response to streptozocin-induced diabetes and in response to a chronic constrictive injury to a nerve leading into the spine;

(g) an isolated polypeptide containing an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence according to any one of (a) to (d), or a variant thereof with sequential amino acid deletions from the C terminus and/or the N-terminus; or

(h) an isolated antibody that binds specifically to the isolated polypeptide according to (g).

[0012] The invention further provides a compound that is useful in the treatment or diagnosis of pain and that modulates the action of an expression product of a gene sequence that becomes down-regulated in the spinal cord of a mammal in response to first and second models of pain, for example being down-regulated both in response to streptozocin induced diabetes and in response to chronic constrictive injury to a nerve leading into the spine.

[0013] The invention also relates to the use of naturally occurring compounds such as peptide ligands of the expression products of the above gene sequences and their associated signal transduction pathways for the treatment of pain.

DESCRIPTION OF PREFERRED EMBODIMENTS

DEFINITIONS

[0014] Within the context of the present invention:

- "Comprising" means consisting of or including. Thus nucleic acid comprising a defined sequence includes nucleic acid that may contain a full-length gene or full-length cDNA. The gene may include any of the naturally occurring regulatory sequence(s), such as a transcription and translation start site, a promoter, a TATA box in the case of eukaryotes, and transcriptional and translational stop sites. Further, nucleic acid comprising a cDNA or gene may include any appropriate regulatory sequences for the efficient expression thereof *in vitro*.
- "Isolated" requires that the material be removed from its original environment (e.g. the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or a peptide present in a living animal is not isolated, but the same polynucleotide or peptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide can be part of a vector and/or such polynucleotide or peptide can

be part of a composition, and still be isolated in that the vector or composition is not a part of its natural environment.

- "Mechanistically distinct" in relation to pain models implies that the pain is induced by mechanisms that differ in kind rather than being variants of a similar pain model. Thus diabetic pain and chronic constrictive pain models are mechanistically distinct, whereas spinal nerve ligation models and sciatic nerve ligation models which both work by ligation are not.
- "Purified" does not require absolute purity; instead it is intended as a relative definition. Purification of starting materials or natural materials from their native environment to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.
- "Nucleic acid sequence" or "gene sequence" means a sequence of nucleotides or any variant or homologue thereof, or truncated or extended sequence thereof, and is preferably indicated by a Genebank accession number. Also within the scope of the present invention are down-regulated nucleic acid sequences which encode expression products which are components of signaling pathways. This invention also includes any variant or homologue or truncated or extended sequence of the down-regulated nucleotide sequence. Also within the scope of the present invention, the term "nucleic acid(s) product", or "expression product" or "gene product" or a combination of these terms refers without being biased, to any, protein(s), polypeptide(s), peptide(s) or fragment(s) encoded by the down-regulated nucleotide sequence.
- "Operably linked" refers to a linkage of polynucleotide elements in a functional relationship. For instance, a promoter or an enhancer is operably linked to a coding sequence if it regulates the transcription of the coding sequence. In particular, two DNA molecules (such as a polynucleotide containing a promoter region, and a polynucleotide encoding a desired polypeptide) are said to be "operably linked" if the nature of the linkage between the two polynucleotides does not (1) result in the introduction of a frame-shift mutation and (2) interfere with the ability of the polynucleotide containing the promoter to direct the transcription of the coding polynucleotide.

"Gene product" refers to polypeptide - which is interchangeable with the term protein - which is encoded by a nucleotide sequence and includes single-chain polypeptide molecules as well as multiple-polypeptide complexes where individual constituent polypeptides are linked by covalent or non-covalent means. Polypeptides of the present invention may be produced by synthetic means (e.g. as described by Geysen *et al.*, 1996) or by recombinant means.

The terms "variant", "homologue", "fragment", "analogue" or "derivative" in relation to the amino acid sequence for the polypeptide of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid from or to the sequence providing the resultant polypeptide has the native gene product activity. In particular, the term "homologue" covers homology with respect to structure and/or function. With respect to sequence homology, there is at least 90%, more preferably at least 95% homology to an amino acid sequence encoded by the relevant nucleotide sequence shown in Tables I - VI, preferably there is at least 98% homology.

Typically, for the variant, homologue or fragment of the present invention, the types of amino acid substitutions that could be made should maintain the hydrophobicity/hydrophilicity of the amino acid sequence. Amino acid substitutions may include the use of non-naturally occurring amino acid analogues.

In addition, or in the alternative, the protein itself could be produced using chemical methods to synthesize a polypeptide, in whole or in part. For example, peptides can be synthesized by solid phase techniques, cleaved from the resin, and purified by preparative high performance liquid chromatography (e.g. Creighton (1983) *Proteins Structures and Molecular Principles*, WH Freeman and Co., New York, NY, USA). The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g. the Edman degradation procedure).

Direct peptide synthesis can be performed using various solid-phase techniques (Roberge JY *et al* *Science* Vol 269 1995 202-204) and automated synthesis may be achieved, for example, using the ABI 431 A Peptide Synthesizer (Perkin Elmer) in accordance with the instructions provided by the manufacturer. Additionally, the amino acid sequence of a gene product, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with a sequence from other subunits, or any part thereof, to produce a variant polypeptide.

In another embodiment of the invention, a gene product natural, modified or recombinant amino acid sequence may be ligated to a heterologous sequence to encode a fusion protein. For example, for screening of libraries for compounds and peptide agonists and antagonists of gene product activity, it may be useful to encode a chimeric gene product expressing a heterologous epitope that is recognised by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between a gene product sequence and the heterologous protein sequence, so that the gene product may be cleaved and purified away from the heterologous moiety.

The gene product may also be expressed as a recombinant protein with one or more additional polypeptide domains added to facilitate protein purification. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilised metals (Porath J, Protein Expr Purif Vol 3 1992 p263-281), protein A domains that allow purification on immobilised immunoglobulin, and the domain utilised in the FLAGS extension/affinity purification system (Immunex Corp, Seattle, WA, USA). The inclusion of a cleavable linker sequence such as Factor XA or enterokinase (Invitrogen, San Diego, CA, USA) between the purification domain and the gene product is useful to facilitate purification.

- "Pain" includes chronic pain, neuropathic pain, pain arising from central sensitisation, and in particular diabetic pain.
- "Stringent hybridization conditions" is a recognized term in the art and for a given nucleic acid sequence refers to those conditions which permit hybridization of that sequence to its complementary sequence and closely homologous sequences. Conditions of high stringency may be illustrated in relation to filter-bound DNA as for example 2X SSC, 65°C (where SSC = 0.15M sodium chloride, 0.015M sodium citrate, pH 7.2), or as 0.5M NaHPO₄, 7% sodium dodecyl sulfate (SDS), 1mM EDTA, at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. *et al.*, eds, 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc., and John Wiley & Sons Inc., New York, at p. 2. 10.3). Hybridization conditions can be rendered highly stringent by raising the temperature and/or by the addition of increasing amounts of formamide, to destabilize the hybrid duplex of non-homologous nucleic acid sequence relative to homologous and closely homologous nucleic acid sequences. Thus, particular hybridisation conditions can be readily manipulated, and will generally be chosen depending on the desired results.
- "Variants or homologues" include (a) sequence variations of naturally existing gene(s) resulting from polymorphism (s), mutation(s), or other alteration(s) as compared to the above identified sequences, and which do not deprive the encoded protein of function (b) recombinant DNA molecules, such as cDNA molecules encoding genes indicated by the relevant Genbank accession numbers and (c) any sequence that hybridizes with the above nucleic acids under stringent conditions and encodes a functional protein or fragment thereof.

IDENTIFIED SEQUENCES

[0015] The inventors have identified nucleotide sequences that give rise to expression products listed in Tables I - VI, that become differentially expressed in the spinal cord in response to two distinct chronic pain stimuli, for example neuropathic and/or central sensitization pain stimuli, and that are believed to be involved in the transduction of pain. In Tables I - VI, * denotes more preferred nucleic acid sequences and ** denotes most preferred nucleic acid sequences. These nucleic acid sequences have not previously been implicated in the transduction of pain.

[0016] The validity of the present experimental procedure was confirmed by the fact that nucleotide sequences were obtained as a result of the investigation whose function in the transduction of pain has been previously confirmed and established. These nucleic acid sequences are not part of this invention. Any of the nucleic acid sequences and expression products can be used to develop screening technologies for the identification of novel molecules for the prevention or treatment of pain. These screening technologies could also be used to ascribe new pain therapeutic indications to molecules that have not previously been identified as being useful for the prevention or treatment of pain. Furthermore, the said nucleic acid sequences can be used as diagnostic tools and for the development of diagnostic tools.

Table I -

Sequences whose expression products are kinases					
Expression product or name (Reference)	Rat Accession Number	Mouse accession number	Human Accession Number	Reaction	Assay
Pyruvate kinase, M1 and M2 subunits (Refs : 1 - 2)	M24359 (SEQ ID No's 1-3)	X97047	X56494	Tissue-specific promoter; Carbohydrate kinase	Kinase

Table II -

Sequences whose expression products are receptors					
Expression Product or Name (Reference)	Rat Accession Number	Mouse accession Number	Human Accession Number	Reaction	Assay
Dopamine receptor D.sub. 1** (Ref : 3)	I58000 (SEQ ID NO 4)			Dopamine receptor	Receptor
Putative GABA-B1a receptor** (Ref : 4)		AF114168 (SEQ ID No's 5-6)		GABA-B Receptor	Receptor

Table III -

Sequences whose expression products are transporters					
Expression Product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Reaction	Assay
Differentiation-associated Na-dependent inorganic phosphate cotransporter (Ref : N/A)	AF271235 (SEQ ID NO's 7-8)			Trans-membrane phosphate transport	Transporter
Putative vacuolar assembly protein VSP41 gene (Ref : N/A)	U87309		AAM47563. 1 (SEQ ID No 9)	Vacuolar assembly and traffic	Transporter

Table IV -

Sequences whose expression products are G-protein coupled receptor proteins					
Expression product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Function	Assay
Git1 (G-protein-coupled receptor kinase-interactor 1 ; GPCR kinase-associated ADP-ribosylation factor) (Ref : 5)	AF085693 (SEQ ID NO 10-11)			Regulation of activity of ARF6 in phosphatidylinositol 3-kinase signalling pathways ; β 2 adrenergic receptor regulation	Ligand binding

Table V -

Sequences whose expression products are DNA-binding proteins

Expression Product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Reaction	Assay
Putative histone H3.3A (Ref: 6)		X91866	M11354(SEQ ID NO 12-13)	DNA binding	DNA binding

Table VI -

Sequences whose expression products are other enzymes

Expression product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Reaction	Assay
3-Hydroxy 3-methylglutaryl coenzyme A synthase, cytosolic * (Ref: 7)	X52625 (SEQ ID No's 14-15)			Cholesterol biosynthesis	Ligase
Acyl-CoA synthetase II, brain (Ref : N/A)	D360666 (N/A)			Fatty acid metabolism	Ligase
Farnesyl diphosphate synthase ** (Ref : 8)	M34477 (Seq ID No's 16-17)			Isoprene biosynthesis	Ligase
Bendless protein (Ref : N /A)	AB032739 (Seq ID No's 18-19)		E12457	Protein degradation	Ligase
fatty acid synthase (Ref: 9)	X62888 (SEQ ID No's 20-21)			Fatty acid synthesis	Ligase
Glutamine synthetase (EC 6.3.1.2) ** (Ref : 10)	M91652 (SEQ ID NO's 22-23)			Amino acid metabolism	Ligase
Putative seryl-tRNA synthetase (Ref No : 11)			X91257 (SEQ ID NO's 24-25)	Ligase	Ligase
Enolase, alpha alpha, non-neuronal (NNE) (REF NO 12)	X02610	X52379	M14328 (SEQ ID NO's 26-27)	Glycolysis	Lyase
Aldose reductase, lens (AREC 11.1.21) (REF : 13)	X05884 (SEQ ID NO's 28-29)			Reduces carbonyl	Oxidoreductase
Cytochrome-c oxidase I, mitochondrial (Ref : 14)	S79304 (SEQ ID NO's 30-31)			Mitochondrial energy metabolism	Oxidoreductase

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Reaction	Assay
Lactate dehydrogenase-B (LDH-B) (Ref : 15)	U07181 (SEQ ID NO's 32-33)	X51905	Y00711	Glycolysis	Oxidoreductase
Putative cytochrome c oxidase VIB (EC 1.9.3.1) (Ref : 16)			X13923 (SEQ ID NO's 34-35)	Mitochondrial energy metabolism	Oxidoreductase
Putative NADH: ubiquinone oxidoreductase PG IV subunit (Ref : 17)			AF044953 (SEQ ID No's 36-37)	Mitochondrial energy metabolism	Oxidoreductase
Putative succinate dehydrogenase flavoprotein (Ref: N/A)		AF095938 (SEQ ID No's 38-39)	AF171022	TCA cycle	Oxidoreductase
Putative ubiquinol-cytochrome-c reductase (EC 1.10.2.2) core protein II (REF: 18)			J04973 (SEQ ID No's 40-41)	Mitochondrial energy metabolism	Oxidoreductase
Stearoyl-coA desaturase 2 * (Ref: N/A)	AB032243 (SEQ ID NO's 42-43)	M26270		Fatty acid biosynthesis	Oxidoreductase
Ribophorin I * (Ref: 19)	X05300 (SEQ ID No's 44-45)			Glycosylation	Transferase
Sulfotransferase-like protein (REF : 20)	AF188699 (SEQ ID No's 46-47)			Transferase	Transferase
ATP synthase, H ⁺ , alpha subunit, mitochondrial (EC 3.6.1.34) (Ref: N/A)	X56133 (SEQ ID No's 48-49)			Mitochondrial energy metabolism	Hydrolase
F1F0 ATPase delta subunit (REF : 21)	U00926 (SEQ ID No's 50-51)			Mitochondrial energy metabolism	Hydrolase
Putative dihydropyrimidinase related protein * (REF: 22)			D78013 (SEQ ID NO's 52-53)	Pyrimidine degradation	Hydrolase
Heat shock protein 90 (REF : 23)	S45392 (SEQ ID NO's 114-115)	M18186	M16660	Cell protection	Hydrolase

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Reaction	Assay
Myelin basic protein S (MBP S) (REF :24)	K00512 SEQ ID No 54)			Myelin structural protein	Ligand binding
Transferrin (Ref 25)	D38380 (SEQ ID No's 55-56)			Iron transport	Ligand binding
Neurofilament, light molecular weight (NF-L) (Ref : 26)	AF031880 (SEQ ID No's 57-58)			Cytoskeleton	Ligand binding
Myelin-associated glycoprotein (MAG) (Ref : 27)	M1680 (SEQ ID NO's 59-60)	M31811		Cell adhesion molecule for postnatal neural development	Ligand binding
NF-M middle molecular weight neurofilament protein (Ref : 28)	M18628 (SEQ ID No's 61-62)			Cytoskeleton	Ligand binding
Neuro-degeneration associated-protein 1 (Ref: 29)	D32249 (SEQ ID No's 63-64)			Protein sorting; synaptic communication and plasticity	Ligand binding
S-100 protein β -subunit (REF: 30)	X01090 (SEQ ID No 65)			Zinc and calcium binding	Ligand binding
Microtubule-associated protein 1b (Map 1b) (Ref: 31)	X60370 (SEQ ID No's 66-67)		L06237	Cytoskeleton protein, neuronal growth/ regeneration; microtubule binding protein	Ligand binding
Putative cdc 37 homolog (Ref: 32)	D26564 (Seq ID No's 68-69)			Cell signalling ; cell cycle protein	Ligand binding
Putative ras-related protein Rab-5c (Ref : 33)			U11293 (SEQ ID No's 70-71)	Small GTP binding protein	Ligand binding
Putative gelsolin (Ref: 34)		J04953 (SEQ ID No's 72-73)		Cytoskeleton protein	Ligand binding
Cd81 antigen (target of antiproliferative antibody 1) (Ref : 35)	U19894 (SEQ ID No's 74-75)	X59047	M33680	Regulator for neuron-induced astrocyte differentiation; microglial effector functions	Ligand binding

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Reaction	Assay
Mobp81 (Myelin-associated/Oligodendrocytic basic protein 81) (Ref : 36)	X87900 (SEQ ID No's 76-77)			Myelin compaction	Ligand binding
Syntaxin binding protein n-sec1, sec1 homolog (Ref : N/A)			BC002869 (Seq ID No's 78-79)	Neuro-transmission	Ligand binding
Alpha-internexin (Ref: 37)	M73049 (SEQ ID No's 80-81)			Cytoskeleton protein; neuronal intermediate filament that can self-assemble	Ligand binding
Putative β -sarcoglycan A3b (Ref: N/a)		AB024921 (SEQ ID No's 82-83)		Cytoskeleton protein	Ligand binding
CGI-78 protein (Ref: 38)	AF151835		AF151835 (SEQ ID No's 84-85)	Unknown	Ligand binding
KIAA0143 (Ref: 39)			D63477 (SEQ ID NO's 86-87)	Transmembrane protein	Ligand binding
Septin 2 (KIAA0128 ; Ref 39)			D50918 (SEQ ID No's 88-89)	GTPase; cytokinesis	Ligand binding
Nucleobindin (Ref: 40)	Z36277 (SEQ ID No's 90-91)			Unknown	Ligand binding
Myelin protein SR13 (Ref: 41)	M69139 (SEQ ID NO's 92-93)	S55427		Myelin structural protein	Ligand binding
B-Actin, cytoplasmic (Ref: 42)	V01217 (SEQ ID NO's 94-95)	X03672		Structural protein	Ligand binding
Ly6/neurotoxin (Lynx1) homolog (Ref: 43)		AF141377 (SEQ ID No's 96-97)		Neuro-transmitter modulator	Ligand binding
Astrocytic phosphoprotein; PFA 15 gene (Ref: N/A)	AJ243949 (SEQ ID NO's 98-99)	X86694		PKC substrate	Ligand binding
PLIC-1 (Ref: N/A)		AF177345 (SEQ ID NO 100-101)		Cytoskeleton interaction	Ligand binding
Nfx1 (tip associating protein (TAP) gene) (Ref: N/A)	AF093139 (SEQ ID NO's 102-103)	AF093140		Unknown	Logand binding

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	Rat Accession Number	Mouse Accession Number	Human Accession Number	Reaction	Assay
Alpha-Crystallin B (Ref N/A)	U04320 (SEQ ID NO's 104-105)	M73741	M28638	Stress response ; heat shock element	Ligand binding
Heat shock-like protein 70 kD (Ref : 44)	X70065 (SEQ ID No's 106-107)	U73744	Y00371	Stress response	Ligand binding
Tau microtubule-associated protein (Ref : 45)	X79321 (SEQ ID NO's 108-109)			Microtubule associated protein expressed in neurons	Ligand binding
Myelin, Schwann cell, Peripheral (P-0) (Ref : 46)	K03242 (SEQ ID No's 110-111)			Myelin structural protein	Ligand binding
B-Tubulin class 1 (Ref: 47)	AB011679 (SEQ ID NO's 112-113)	X04663	AF14139	Structural protein	Ligand binding
Putative ribonuclease III (Ref : N/A)			AF116910 (SEQ ID NO's 116-117)	RNA hydrolysis	Hydrolase

PRODUCTION OF POLYPEPTIDES AND NUCLEIC ACIDS

Vectors

[0017] Recombinant expression vectors comprising a nucleic acid can be employed to express any of the nucleic acid sequences of the invention. The expression products derived from such vector constructs can be used to develop screening technologies for the identification of molecules that can be used to prevent or treat pain, and in the development of diagnostic tools for the identification and characterization of pain. The expression vectors may also be used for constructing transgenic non-human animals.

[0018] Gene expression requires that appropriate signals be provided in the vectors, said signals including various regulatory elements such as enhancers/promoters from viral and/or mammalian sources that drive expression of the genes or nucleic acid sequences of interest in host cells. The regulatory sequences of the expression vectors used in the invention are operably linked to the nucleic acid sequence encoding the pain-associated protein of interest or a peptide fragment thereof.

[0019] Generally, recombinant expression vectors include origins of replication, selectable markers, and a promoter derived from a highly expressed gene to direct transcription of a downstream nucleotide sequence. The heterologous nucleotide sequence is assembled in an appropriate frame with the translation, initiation and termination sequences, and if applicable a leader sequence to direct the expression product into the periplasmic space, the extra-cellular medium or cell membrane.

[0020] In a specific embodiment wherein the vector is adapted for expressing desired sequences in mammalian host cells, preferred vectors will comprise an origin of replication from the desired host, a suitable promoter and an enhancer, and also any necessary ribosome binding sites, polyadenylation site, transcriptional termination sequences, and optionally 5'-flanking non-transcribed sequences. DNA sequences derived from the SV40 or CMV viral genomes, for example SV40 or CMV origin, early promoters, enhancers, and polyadenylation sites may be used to provide the required non-transcribed genetic elements.

[0021] A recombinant expression vector used in the invention advantageously also comprises an untranscribed poly-

nucleotide region located at the 3' end of the coding sequence (ORF), this 3'-UTR (untranslated region) polynucleotide being useful for stabilizing the corresponding mRNA or for increasing the expression rate of the vector insert if this 3'-UTR harbours regulation signal elements such as enhancer sequences.

[0022] Suitable promoter regions used in the expression vectors are chosen taking into account the host cell in which the nucleic acid sequence is to be expressed. A suitable promoter may be heterologous with respect to the nucleic acid sequence for which it controls the expression, or alternatively can be endogenous to the native polynucleotide containing the coding sequence to be expressed. Additionally, the promoter is generally heterologous with respect to the recombinant vector sequences within which the construct promoter/coding sequence has been inserted. Preferred promoters are the LacI, LacZ, T3 or T7 bacteriophage RNA polymerase promoters, the lambda PR, PL and Trp promoters (see EP-0 036 776), the polyhedrin promoter, or the p10 protein promoter from *baculovirus* (kit Novagen; Smith *et al.*, (1983); O'Reilly *et al.* (1992)).

[0023] Preferred selectable marker genes contained in the expression recombinant vectors used in the invention for selection of transformed host cells are preferably dehydrofolate reductase or neomycin resistance for eukaryotic cell culture, TRP1 for *S. cerevisiae* or tetracycline, rifampicin or ampicillin resistance in *E. coli*, or Levamsaccharase for *Mycobacteria*, this latter marker being a negative selection marker.

[0024] Preferred bacterial vectors are listed hereafter as illustrative but not limitative examples: pQE70, pQE60, pQE-9 (Quiagen), pD10, phagescript, psiX174, p.Bluescript SK, pNH8A, pNH16A, pNH18A, pNH46A (Stratagene); pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia); pWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene); pSVK3, pBPV, pMSG, pSVL (Pharmacia); pQE-30 (QIA express).

[0025] Preferred bacteriophage recombinant vectors of the invention are P1 bacteriophage vectors such as described by Sternberg N.L. (1992;1994).

[0026] A suitable vector for the expression of any of the pain associated polypeptides used in the invention or fragments thereof, is a baculovirus vector that can be propagated in insect cells and in insect cell-lines. A specific suitable host vector system is the pVL 1392/1393 *baculovirus* transfer vector (Pharmingen) that is used to transfect the SF9 cell line (ATCC N°CRL 1711) that is derived from *Spodoptera frugiperda*.

[0027] The recombinant expression vectors of the invention may also be derived from an adenovirus. Suitable adenoviruses are described by Feldman and Steig (1996) or Ohno *et al.* (1994). Another preferred recombinant adenovirus is the human adenovirus type two or five (Ad 2 or Ad 5) or an adenovirus of animal origin (Patent Application WO 94/26914)

[0028] Particularly preferred retrovirus for the preparation or construction of retroviral *in vitro* or *in vivo* gene delivery vehicles include retroviruses selected from the group consisting of Mink-Cell Focus Inducing Virus, Murine Sarcoma Virus, and Ross Sarcoma Virus. Other preferred retroviral vectors are those described in Roth *et al.* (1996), in PCT Application WO 93/25234, in PCT Application WO 94/06920, and also in Roux *et al.* (1989), Julian *et al.* (1992) and Nada *et al.* (1991).

[0029] Yet, another viral vector system that is contemplated is the Adeno Associated Viruses (AAV) such as those described by Flotte *et al.* (1992), Samulski *et al.* (1989) and McLaughlin *et al.* (1996).

Host cells expressing pain associated polypeptides

[0030] Host cells that endogenously express pain associated polypeptides or have been transformed or transfected with one of the nucleic acid sequences described herein, or with one of the recombinant vector described above, particularly a recombinant expression vector, can be used in the present invention. Also included are host cells that are transformed (prokaryotic cells) or are transfected (eukaryotic cells) with a recombinant vector such as one of those described above.

[0031] Preferred host cells used as recipients for the expression vectors used in the invention are the following:

(a) prokaryotic host cells: *Escherichia coli*, strains. (i.e. DH5- α , strain) *Bacillus subtilis*, *Salmonella typhimurium* and strains from species like *Pseudomonas*, *Streptomyces* and *Staphylococcus* for the expression of up and down-regulated nucleic acid sequence modulated by pain, characterized by having at least 80% sequence identity with any of the nucleic acid sequences of Tables I - VI. Plasmid propagation in these host cells can provide plasmids for transfecting other cells.

(b) eukaryotic host cells: HeLa cells (ATCC N°CCL2; N°CCL2.1; N°CCL2.2), Cv 1 cells (ATCC N°CCL70), COS cells (ATCC N°CRL 1650; N°CRL 1651), Sf-9 cells (ATCC N°CRL 1711), C127 cells (ATCC N°CRL-1804), 3T3 cells (ATCC N°CRL-6361), CHO cells (ATCC N°CCL-61), human kidney 293 cells (ATCC N° 45504; N°CRL-1573), BHK (ECACC N°84100 501; N°84111301); PC12 (ATCC N° CRL-1721), NT2, SHSYSY (ATCC N° CRL-2266), NG108 (ECACC N°88112302) and F11, SK-N-SH (ATCC N° CRL-HTB-11), SK-N-BE(2) (ATCC N° CRL-2271), IMR-32 (ATCC N° CCL-127). A preferred system to which the nucleic acids of the invention can be expressed are

neuronal cell lines such as PC12, NT2, SHSY5Y, NG108 and F11, SK-N-SH, SK-N-BE(2), IMR-32 cell lines, COS cells, 3T3 cells, HeLa cells, 292 cells and CHO cells. The above cell lines could be used for the expression of any of the nucleic acid sequences of Tables I - VI.

[0032] When a nucleic acid sequence of any of Tables I - X is expressed using a neuronal cell line, the sequence can be expressed through an endogenous promoter or native neuronal promoter, or an exogenous promoter. Suitable exogenous promoters include SV40 and CMV and eukaryotic promoters such as the tetracycline promoter. The preferred promoter when pain associated molecules are endogenously expressed is an endogenous promoter. A preferred promoter in a recombinant cell line is the CMV promoter.

[0033] In a specific embodiment of the host cells described above, these host cells have also been transfected or transformed with a polynucleotide or a recombinant vector for the expression of a natural ligand of any of the nucleic acid sequences of any of Tables I - VI or a modulator of these expression products.

PROTEINS, POLYPEPTIDES AND FRAGMENTS

[0034] The expression products of the nucleic acid sequences of Tables I - VI or fragment(s) thereof can be prepared using recombinant technology, from cell lines or by chemical synthesis. Recombinant methods, chemical methods or chemical synthetic methods can be used to modify a gene in order to introduce into the gene product, or a fragment of the gene product, features such as recognition tags, cleavage sites or other modifications. For efficient polypeptide production, the endogenous expression system or recombinant expression system should allow the expression products to be expressed in a manner that will allow the production of a functional protein or fragment thereof which can be purified. Preferred cell lines are those that allow high levels of expression of polypeptide or fragments thereof. Such cell lines include cell lines which naturally express the nucleic acid sequence of Tables I - VI or common mammalian cell lines such as CHO cells or COS cells, etc, or more specific neuronal cell lines such as PC12. However, other cell types that are commonly used for recombinant protein production such as insect cells, amphibian cells such as oocytes, yeast and prokaryotic cell lines such as *E. coli* can also be used.

[0035] The expression products of Tables I - VI or fragments thereof can be utilized in screens to identify potential therapeutic ligands, either as a purified protein, as a protein chimera such as those produced in phage display, as a cell membrane (lipid or detergent) preparation, or in intact cells.

[0036] The invention also relates generally to the use of proteins, peptides and peptide fragments for the development of screening technologies for the identification of molecules for the prevention or treatment of pain, and the development of diagnostic tools for the identification and characterization of pain. These peptides include expression products of the nucleic acid sequences of Tables I - VI and purified or isolated polypeptides or fragments thereof having at least 90%, preferably 95%, more preferably 98% and most preferably 99% sequence identity with the any of the expression products of nucleic acid sequences of Tables I - VI. Expressed peptides and fragments of any of these nucleic acid sequences can be used to develop screening technologies for the identification of novel molecules for the prevention or treatment of pain. These screening technologies could also be used to ascribe new pain therapeutic indications to molecules, which have not previously been ascribed for the prevention or treatment of pain. Furthermore the said expressed peptides and fragments can be used as diagnostic tools and for the development of diagnostic tools.

SCREENING METHODS

[0037] As discussed above, we have identified nucleic acid sequences whose expression is regulated by pain, particularly chronic pain and more particularly diabetic pain. The expression products of these nucleic acids can be used for screening ligand molecules for their ability to prevent or treat pain, and particularly, but not exclusively, chronic pain. The main types of screens that can be used are described below. The test compound can be a peptide, protein or chemical entity, either alone or in combination(s), or in a mixture with any substance. The test compound may even represent a library of compounds.

[0038] The expression products of any of the nucleic acid sequences of Tables I - VI or fragments thereof can be utilized in a ligand binding screen format, a functional screen format or *in vivo* format. Examples of screening formats are provided.

A) Ligand binding screen

[0039] In ligand binding screening a test compound with is contacted with an expression product of one of the sequences of Tables I - VI, and the ability of said test compound to interact with said expression product is determined, e.g. the ability of the test compound(s) to bind to the expression product is determined. The expression product can be a part of an intact cell, lipidic preparation or a purified polypeptide(s), optionally attached to a support, such as

beads, a column or a plate etc.

[0040] Binding of the test compound is preferably performed in the presence of a ligand to allow an assessment of the binding activity of each test compound. The ligand may be contacted with the expression product either before, simultaneously or after the test compound. The ligand should be detectable and/or quantifiable. To achieve this, the ligand can be labelled in a number of ways, for example with a chromophore, radioactive, fluorescent, phosphorescent, enzymatic or antibody label. Methods of labelling are known to those in the art. If the ligand is not directly detectable it should be amenable to detection and quantification by secondary detection, which may employ the above technologies. Alternatively the expression product or fragment thereof can be detectable or quantifiable. This can be achieved in a similar manner to that described above.

[0041] Binding of the test compound modifies the interaction of the ligand with its binding site and changes the affinity or binding of the ligand for/to its binding site. The difference between the observed amount of ligand bound relative to the theoretical maximum amount of ligand bound (or to the ligand bound in the absence of a test compound under the same conditions) is a reflection of the binding ability (and optionally the amount and/or affinity) of a test compound to bind the expression product.

[0042] Alternatively, the amount of test compound bound to the expression product can be determined by a combination of chromatography and spectroscopy. This can be achieved with technologies such as Biacore (Amersham Pharmacia). The amount of test compound bound to the expression product can also be determined by direct measurement of the change in mass upon compound or ligand binding to the expression product. Alternatively, the expression product, compound or ligand can be fluorescently labelled and the association of expression product with the test compound can be followed by changes in Fluorescence Energy Transfer (FRET).

[0043] The invention therefore includes a method of screening for pain alleviating compounds, comprising:

- a) contacting a test compound or test compounds in the presence of a ligand with an expression product of any of the nucleic acid sequences of Tables I - VI or with a cell expressing at least one copy of the expression product or with a lipidic matrix containing at least one copy of the expression product;
- b) determining the binding of the test compound to the expression product, and
- c) selecting test compounds on the basis of their binding abilities.

[0044] In the above method, the ligand may be added prior to, simultaneously with or after contact of the test compound with the expression product. Non limiting examples and methodology can be gained from the teachings of the *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA), *Methods in neurotransmitter receptor analysis* (Yamamura HI., Enna, SJ., and Kuhar, MJ., Raven Press New York, the *Glaxo Pocket Guide to Pharmacology*, Dr. Michael Sheehan, Glaxo Group Research Ltd, Ware, Herts SG12 0DP), *Bylund DB and Murrin LC* (2000, Life Sciences, 67 (24) 2897-911), *Owicki JC* (2000, *J. biomol Screen* (5) 297-306), *Alberts et al* (1994, *Molecular Biology of the Cell*, 3rd Edn, Garland Publication Inc), *Butler JE*, (2000 *Methods* 22(1):4-23, *Sanberg SA* (2000, *Curr Opin Biotechnol* 11(1) 47-53), and *Christopoulos A* (1999, *biochem Pharmacol* 58(5) 735-48).

B) Functional screening

(a) Kinase assays

[0045] The expression product of any of the nucleic acid sequences of Tables I - VI which encode a kinase, and in particular the nucleic acid sequence listed in Table I, is amenable to screening using kinase assay technology.

[0046] Kinases have the ability to add phosphate molecules to specific residues in ligands such as binding peptides in the presence of a substrate such as adenosine triphosphate (ATP). Formation of a complex between the kinase, the ligand and substrate results in the transfer of a phosphate group from the substrate to the ligand. Compounds that modulate the activity of the kinase can be determined with a kinase functional screen. Functional screening for modulators of kinase activity therefore involves contacting one or more a test compounds with an expression product of one of the nucleic acid sequences of Tables I - VI which encodes a kinase, and determining the ability of said test compound to modulate the transfer of a phosphate group from the substrate to the ligand.

[0047] The expression product can be part of an intact cell or of a lipidic preparation or it can be a purified polypeptide (s), optionally attached to a support, for example beads, a column, or a plate. Binding is preferably performed in the presence of ligand and substrate to allow an assessment of the binding activity of each test compound.

[0048] The ligand should contain a specific kinase recognition sequence and it should not be phosphorylated at its phosphorylation site. The ligand and/or substrate may be contacted with the kinase either before, simultaneously or after the test compound. Optionally the substrate may be labelled with a kinase transferable labelled phosphate. The assay being monitored by the phosphorylation state of the substrate and/or the ligand. The ligand should be such that its phosphorylation state can be determined. An alternative method to do this is to label the ligand with a phosphor-

ylation-state-sensitive molecule. To achieve this, the ligand can be labelled in a number of ways, for example with a chromophore, radioactive, fluorescent, phosphorescent, enzymatic or antibody label. If the ligand is not directly detectable it should be amenable to detection and quantification by secondary detection, which may employ the above technologies. Such technologies are known to those in the art.

[0049] Binding of the test compound to the kinase modifies its ability to transfer a phosphate group from the substrate to the ligand. The difference between the observed amount of phosphate transfer relative to the theoretical maximum amount of phosphate transfer is a reflection of the modulatory effect of the test compound. Alternatively, the degree of phosphate transfer can be determined by a combination of chromatography and spectroscopy. The extent of phosphorylation of the ligand peptide or dephosphorylation of the substrate can also be determined by direct measurement. This can be achieved with technologies such as Biacore (Amersham Pharmacia).

[0050] The invention also provides a method for screening compounds for the ability to relieve pain, which comprises:

- (a) contacting one or more test compounds in the presence of ligand and substrate with an expression product of any of the sequences of Tables I - VI which is a kinase or with a cell containing at least 1 copy of the expression product or with a lipidic matrix containing at least 1 copy of an expression product;
- (b) determining the amount of phosphate transfer from the substrate to the ligand; and
- (c) selecting test compounds on the basis of their capacity to modulate phosphate transfer.

[0051] Optionally ligand, substrate and/or other essential molecules may be added prior to contacting the test compound with expression product of step (a) or after step (a). Non limiting examples and methodology can be gained from the teachings of the *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA), *Methods in Molecular Biology* 2000; 99: 191-201, *Oncogene* 2000 20; 19(49): 5690-701, and *FASAB Journal*, (10, 6, P55, P1458, 1996, Pocius D Amrein K *et al*).

b) Receptor assays

[0052] An expression product of any of the nucleic acid sequences of Tables I - VI which encodes a receptor, and in particular any of the nucleic acid sequences listed in Table II, is amenable to screening using receptor assay technology.

[0053] Receptors are membrane associated proteins that initiate intracellular signalling upon ligand binding. Therefore, the identification of molecules for the prevention and treatment of pain can be achieved with the use of a ligand binding assay, as outlined above. Such an assay would utilize an endogenous or non-endogenous ligand as a component of the ligand binding assay. The binding of this ligand to the receptor in the presence of one or more test compounds would be measured as described above. Such is the nature of receptors that the assay is usually, but not exclusively performed with a receptor as an intact cell or membraneous preparation.

[0054] The invention therefore includes a method of screening for pain alleviating compounds, comprising:

- a) contacting a test compound or test compounds in the presence of a ligand with a cell expressing at least one copy of the expression product of any of the sequences of Tables I - VI which is a receptor or with a lipidic matrix containing at least one copy of the expression product;
- b) determining the binding of the test compound to the expression product, and
- c) selecting test compounds on the basis of their binding abilities.

c) Transporter protein assays

[0055] An expression product of any of the nucleic acid sequences of Tables I - VI which encodes a transporter protein, and in particular any of the nucleic acid sequences listed in Table III, is amenable to screening using transporter protein assay technology. Non limiting examples of technologies and methodologies are given by *Carroll FI, et al* (1995, Medical Research Review, Sep15 (5) p419-444), *Veldhuis JD and Johnson MI* (1994, Neurosci. Biobehav Rep., winter 18(4) 605-12), *Hediger MA and Nussberger S* (1995, Expt Nephrol. July-Aug 3(4) p211-218, *Endou H and Kanai Y*, (1999, Nippon Yakurigaku Zasshi, Oct. 114 Suppl 1:1p-16p), *Olivier B et al* (2000, Prog. Drug Res., 54, 59-119), *Braun A et al* (2000, Eur J Pharm Sci, oct 11, Suppl 2 S51-60) and *Molecular Probes handbook and references therein* (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA).

[0056] The main function of transporter proteins is to facilitate the movement of molecules across a cellular membrane. Compounds that modulate the activity of transporter proteins can be determined with a transporter protein functional screen. Functional screening for modulators of transporter proteins comprises contacting at least one test compound with an expression product as aforesaid which is a transporter protein and determining the ability of said test compound to modulate the activity of said transporter protein. The expression product can be part of an intact cell,

or lipidic preparation, optionally attached to a support, for example beads, a column or a plate. Binding is preferably performed in the presence of the molecule to be transported, which should only be able to pass through a cell membrane or lipidic matrix with the aid of the transporter protein. The molecule to be transported should be able to be followed when it moves into a cell or through a lipidic matrix. Preferably the molecule to be transported is labelled to aid in characterization, e.g. with a chromophore, radioactive, fluorescent, phosphorescent, enzymatic or antibody label. If the molecule to be transported is not directly detectable it should be amenable to detection and quantification by secondary detection, which may employ the above technologies. The molecule to be transported may be contacted with the transporter protein before, simultaneously with or after the test compound. If binding of the test compound to the transporter protein modifies its ability to transport molecules through a membranous or lipidic matrix, then the difference between the observed amount of transported molecule in a cell/or through a lipidic matrix relative to the theoretical maximum amount is a reflection of the modulatory effect of the test compound.

[0057] The invention further provides a method for screening compounds for their ability to relieve pain, comprising

- a) contacting at least one test compound in the presence of transporter molecules with a cell containing at least one copy of an expression product of any of the sequences of Tables I - VI which is a transporter protein or with a lipidic matrix containing at least one copy of the expression product;
- c) measuring the movement of transported molecules into or from the cell, or across the lipidic matrix; and
- d) selecting test compounds on the basis of their ability to modulate the movement of transported molecules.

d) G-protein coupled receptor protein assays

[0058] An expression product of any of the nucleic acid sequences of Tables I - VI that encodes a G-protein coupled receptor protein, and in particular any of the nucleic acid sequences listed in Table IV, is amenable to screening using G-protein coupled receptor protein assay technology.

[0059] G-protein coupled receptor proteins (GPCRs) are membrane associated proteins whose main function is to transduce a signal through a cellular membrane. Upon ligand binding, GPCRs undergo a conformational change that allows complexing of the GPCRs with a G-protein. G-proteins possess a GTP/GDP binding site. The formation of the G-protein/ligand complex allows exchange of GTP for GDP, resulting in a conformational change of the G-protein. This conformational change initiates signal transduction.

[0060] Functional screening for modulators of GPCRs comprises contacting at least one test compound with an expression product as aforesaid which is a G-protein coupled receptor protein, and assessing the ability of the test compound(s) to modulate the exchange of GTP for GDP or the modulation of the GPCR signal transduction pathway. The expression product can be part of an intact cell or lipidic preparation, optionally attached to a support, for example beads, a column or a plate. Binding is preferably performed in the presence of a ligand, G-protein and GTP/GDP to allow an assessment of the binding activity of each test compound. Alternatively components of the signaling pathway are also included. In particular, in a preferred embodiment, a labeled GTP is used and the ability of the test compound(s) to modulate the exchange of GTP to GDP is determined. A further optional characteristic of the assay can be the inclusion of a reporter molecule that enables monitoring the regulation of the signaling pathway. The ligand may be contacted with the GPCR before, simultaneously with, or after the test compound. Binding of the test compound to the GPCR modifies its ability to modulate the exchange of GTP for GDP and hence the modulation of signal transduction. The difference between the observed amount of GTP exchanged for GDP relative to the theoretical maximum amount of GTP is a reflection of the modulatory effect of the test compound. Likewise the relative activities of signal transduction reporter molecules are also a reflection of the modulatory effect of the test compound. Non limiting examples of technologies and methodologies can be found in *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA), *Glaxo Pocket Guide to Pharmacology*, (Michael Sheehan, Pharmacology Division staff, Glaxo Group Research Ltd., Ware, Herts SG12 0DP) and *Xing et al* (2000, J. Recept. Signal. Transduct. Res. 20(40) 189-210).

[0061] The invention provides a method of screening compounds for their ability to relieve pain, comprising:

- a) contacting at least one test compound in the presence of a ligand, GTP/GDP, G-protein with a cell containing at least one copy of an expression product of a sequence of Tables I - VI as aforesaid which is a G-protein coupled receptor protein or with a lipidic matrix containing at least one copy of the expression product;
- b) measuring the exchange of GTP for GDP, and
- c) selecting test compounds on the basis of their ability to modulate said exchange.

In the above method, the ligand, GTP/GDP, G-protein and other essential molecules can be added before, simultaneously with or after the contacting of the test compound(s) with the cell line or lipidic matrix in step (a).

e) DNA-binding protein assays

[0062] An expression product of any of the nucleic acid sequences of Tables I - VI that encodes a DNA-binding protein, and in particular any of the nucleic acid sequences listed in Table V, is amenable to screening using DNA-binding protein assay technology.

[0063] DNA binding proteins are proteins that are able to complex with DNA. The complexing of the DNA binding protein with the DNA in some instances requires a specific nucleic acid sequence. Screens can be developed in a similar manner to ligand binding screens as previously indicated and will utilise DNA as the ligand. DNA-binding protein assays can be carried using similar principles described in ligand binding assays as described above. Non limiting examples of methodology and technology can be found in the teachings of *Haukanes BI and Kvam C* (Biotechnology, 1993 Jan 11 60-63), *Alberts B et al* (Molecular Biology of the Cell, 1994, 3rd Edn., Garland Publications Inc, *Kirigiti P and Machida CA* (2000 Methods Mol Biol, 126, 431-51) and *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave., Eugene, USA).

[0064] The invention therefore includes a method of screening for pain alleviating compounds, comprising:

a) contacting a test compound or test compounds in the presence of a plurality of nucleic acid sequences with an expression product of any of the nucleic acid sequences of Tables I - VI which is a DNA binding protein or with cells expressing at least one copy of the expression product or with a lipidic matrix containing at least one copy of the expression product;

b) determining the binding of the test compound to the expression product, and

c) selecting test compounds on the basis of their binding abilities.

In the above method, the plurality of nucleic acid sequence may be added prior to, simultaneously with or after contact of the test compound with the expression product.

f) Assays using other enzymes

[0065] Expression products of any of the nucleic acid sequences of Tables I - VI that encode other enzymes, e.g. ligases, lyases, oxidoreductases, transferases and hydrolases, and in particular any of the nucleic acid sequences listed in Table VI, is amenable to screening using appropriate assay technology.

[0066] Each class of enzyme has a defined function. Ligases have the property of being able to splice molecules together. This is achieved with the conversion of ATP substrate to AMP. Therefore, the activity of a ligase can be followed by monitoring the conversion of ATP to AMP. Such technologies are known to those in the art. Non limiting examples and methodologies are illustrated by *Ghee. T. Tan et al* (1996, Biochem J. 314, 993-1000, *Yang SW et al* (1992, 15: 89(6) 2227-31 and references therein, and in *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA).

[0067] The invention also provides a methods of screening for pain alleviating compounds, comprising;

a) contacting one or more test compounds in the presence of ATP with an expression product of any of the sequences of Tables I - VI which is a ligase or with a cell expressing at least 1 copy of a expression product or with a lipidic matrix containing at least 1 copy of an expression product which is a ligase;

b):determining the amount of ATP converted to AMP, and

c) selecting test compounds on the basis of their ability to modulate said conversion.

[0068] Lyases are enzymes which catalyse the cleavage of by reactions other than hydrolysis. These enzymes can be grouped into seven groups according to type of bond cleaved. These groups are carbon-carbon lyases (E.C. No 4.1), carbon-oxygene lyases (E.C. No 4.2), carbon-nitrogen lyases (E.C. No 4.3), carbon-sulphur lyase (E.C. No 4.4) carbon-halide lyases (E.C. No 4.5), phosphorous-oxygene lyases (E.C. No 4.6) and other lyases (E.C. No 4.99) (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman press). The enzyme commission number (E.C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further *teachings on how to develop assays and screens for lyases can be obtained from Methods in Enzymology* (Academic Press).

[0069] Oxidoreductases are enzymes that catalyse the transfer of hydrogen or oxygen atoms or electrons. These enzymes can be sub-grouped into twenty categories according to their specific mode of action. These groups are oxidoreductases acting on the CH-OH group of donors (E.C. No.1 oxidoreductases acting on the aldehyde or oxo group of donors (E.C. No 1.2), oxidoreductases acting on the CH-CH group of the donor (E.C. No 1.3), oxidoreductases acting on the CH-NH₂ group of donors (E.C. 1.4), oxidoreductases acting on the CH-NH group of donor (E.C. 1.5), oxidoreductases acting on the NADH or NADPH (E.C. No 1.6), oxidoreductases acting on other nitrogen compounds as donors (E.C. No 1.7), oxidoreductases acting on a sulphur group of donors (E.C. No 1.8), oxidoreductases acting on a haem group of donors (E.C. No1.9), oxidoreductases acting on diphenols and related substances as donors (E.

C. 1.10), oxidoreductases acting on hydrogen peroxide as acceptor (E.C. No 1.11), oxidoreductases acting on hydrogen as donor (E.C. No 1.12), oxidoreductases acting on single donors with incorporation of molecular oxygen (E.C. No 1.13), oxidoreductases acting on paired donors with incorporation of molecular oxygen (E.C. No 1.14), oxidoreductases acting on superoxide radicals as acceptors (E.C. 1.15), oxidoreductases oxidizing metal ions (E.C. No 1.16), oxidoreductases acting on -CH₂ groups (E.C. No 1.17), oxidoreductases acting on reduced ferredoxin as donor (E.C. No 1.18), oxidoreductases acting on reduced flavodoxin as donor (E.C. No 1.19) and other oxidoreductases (E.C. No 1.97) (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman Press). The enzyme commission number (E.C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further teachings on how to develop assays and screens for oxidoreductases can be obtained from *Methods in Enzymology* (Academic Press) with special reference to volume 249.

[0070] Transferases are enzymes that catalyse the transfer of specific groups. They are classified into eight sub groups according to function, transferring one-carbon group (E.C. No 2.1), Transferring aldehyde or ketonic residues (E.C. No 2.2), Acetyltransferases (E.C. 2.3), glycosyltransferases (E.C. No 2.4), transferring alkyl or aryl groups other than methyl groups (E.C. No 2.5), transferring nitrogenous groups (E.C. No 2.6), transferring phosphorous-containing groups (E.C. No 2.7) and transferring sulphur-containing groups (E.C. No 2.8) (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman Press). The enzyme commission number (E.C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further teachings on how to develop assays and screens for transferases can be obtained from *Methods in Enzymology* (Academic Press).

[0071] Hydrolases are enzymes that catalyse hydrolytic reactions and are sub-grouped into eleven classes according to the type of reaction they carry out. Hydrolases acting on ester bonds (E.C. No 3.1), hydrolases acting on glycosyl compounds (E.C. No 3.2), hydrolases acting on ether bonds (E.C. No 3.3), hydrolases acting on peptide bonds (E.C. No 3.4), hydrolases acting on carbon-nitrogen bonds, other than peptide bonds (E.C. No 3.5), hydrolases acting on acid anhydrides (E.C. No 3.6), hydrolases acting on acid anhydrides (E.C. No 3.6), hydrolases acting on carbon-carbon bonds (E.C. No 3.7), hydrolases acting on halide bonds (E.C. No 3.8), hydrolases acting on phosphorous-nitrogen bonds (E.C. No 3.9), hydrolases acting on sulphur-nitrogen bonds (E.C. No 3.10) and hydrolases acting on carbon-phosphorous bonds (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman Press). The enzyme commission number (E.C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further teachings on how to develop assays and screens for hydrolases can be obtained from *Methods in Enzymology* (Academic Press) with special reference to volume 249.

C) In vivo functional screen

[0072] Any of the nucleotide sequences described in Tables I - VI or homologues thereof may be inserted by means of an appropriate vector into the genome of a lower vertebrate or of an invertebrate animal or may be inactivated or down regulated in the genome of said animal. The resulting genetically modified animal may be used for screening compounds for effectiveness in the regulation of pain. The invertebrate may, for example, be a nematode e.g. *Caenorhabditis elegans*, which is a favourable organism for the study of response to noxious stimuli. Its genome sequence has been determined, see *Science*, **282**, 2012 (1998), it can be bred and handled with the speed of a micro-organism (it is a self-fertilizing hermaphrodite) and can therefore be used in a high throughput screening format (WO 00/63424, WO 00/63425, WO 00/63426 and WO 00/63427), and it offers a full set of organ systems, including a simple nervous system and contains many similarly functioning genes and signaling pathways to mammals. A thermal avoidance model based on a reflexive withdrawal reaction to an acute heat stimulus has been described by Wittenburg *et al*, *Proc. Natl. Acad. Sci. USA*, **96**, 10477-10482 (1999), and allows the screening of compounds for the treatment of pain with the modulation of pain sensation as an endpoint.

[0073] The genome of *C. elegans* can be manipulated using homologous recombination technology which allows direct replacement of nucleic acids encoding *C. elegans* with their identified mammalian counterpart. Replacement of these nucleic acids with those nucleic acids outlined above would allow for the direct screening of test compound(s) with their expression products. Any of the pain-related genes described above may be ligated into a plasmid and introduced into oocytes of the worm by microinjection to produce germline transformants. Successful plasmid injection into *C. elegans* and expression of inserted sequences has been reported by Devgen B.V., Ghent, Belgium. It is also possible to produce by routine methods worms in which the target sequences are down-regulated or not expressed (knock-out worms). Further non limiting examples of methodology and technology can be found in the teachings of Hazendonk *et al* (1997, *Nat genet.* 17(1) 119-21), Alberts *et al*, (1994, *Molecular Biology of the Cell* 3rd Ed. Garland Publishing Inc, *Caenorhabditis elegans* is anatomically and genetically simple), Broverman S *et al*, (1993, *PNAS USA* 15;90(10) 4359-63) and Mello *et al* (1991, 10(12)3959-70).

[0074] A further method for screening compounds for ability to modify response to pain, e.g. relieve pain, comprises:

- (a) contacting one or more test compounds with at least one *C. elegans* containing at least one copy of a sequence

as set out above;

(b) subjecting the *C. elegans* to a nociceptive stimulus;

(c) observing the response of the *C. elegans* to said stimulus; and

d) selecting test compounds on the basis of their ability to modify the response of *C. elegans* to said stimulus.

DIAGNOSTIC TOOLS AND KITS

Affinity peptides, ligands and substrates

[0075] Pain associated polypeptides and fragments thereof can be detected at the tissue and cellular levels with the use of affinity peptides, ligands and substrates, which will enable a skilled person to define more precisely a patient's ailment and help in the prescription of a medicament. Such affinity peptides are characterized in that firstly they are able to bind specifically to a pain associated polypeptide, and secondly that they are capable of being detected. Such peptides can take the form of a peptide or polypeptide for example an antibody domain or fragment, or a peptide/polypeptide ligand or substrate, or a polypeptide complex such as an antibody.

[0076] The preparation of such peptides and polypeptides are known to those in the art. Antibodies, these may be polyclonal or monoclonal, and include antibodies derived from immunized animals or from hybridomas, or derivatives thereof such as humanized antibodies, Fab or F(ab')₂ antibody fragments or any other antibody fragment retaining the antigen binding specificity.

[0077] Antibodies directed against pain-associated gene product molecules may be produced according to conventional techniques, including the immunization of a suitable mammal with the peptides or polypeptides or fragment thereof. Polyclonal antibodies can be obtained directly from the serum of immunized animals. Monoclonal antibodies are usually produced from hybridomas, resulting from a fusion between splenocytes of immunized animals and an immortalized cell line (such as a myeloma). Fragments of said antibodies can be produced by protease cleavage, according to known techniques. Single chain antibodies can be prepared according to the techniques described in US 4,946,778. Detection of these affinity peptides could be achieved by labeling technologies which allow detection of peptides, such as enzymatic labeling, fluorescence labeling or radio-labeling are well known to those in the art. Optionally these affinity peptides, ligands and substrates could themselves be detected with the use of a molecule that has specific affinity to the peptides, ligands and substrates and is itself labeled.

[0078] The invention further provides a kit comprising;

(a) affinity peptide and/or ligand and/or substrate for an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain ; and

(b) a defined quantity of an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal both in response to first and second models of neuropathic or central sensitization pain, for simultaneous, separate or sequential use in detecting and/or quantifying an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

Complimentary nucleic acids

[0079] Pain associated nucleic acid sequences can be characterized at the tissue and cellular levels with the use of complimentary nucleic acid sequences. Detection of the level of expression of pain associated nucleic acid sequences can help in the prognosis of a pain condition and the prescription of a medicament. These complimentary nucleic acids are characterized in that they can hybridize to a pain associated nucleic acid sequence and their presence can be detected through various techniques. Such techniques are known to those in the art and may include detection by polymerase chain reaction or detection by labeling of complimentary nucleic acid sequences by enzymatic labeling, affinity labeling fluorescent labeling or radio labeling. Complimentary strand nucleic acid sequences of this invention are 10 to 50 bases long, more preferably 15 to 50 bases long and most preferably 15 to 30 bases long, and hybridize to the coding sequence of the nucleic acid sequence.

[0080] A further aspect of this invention is a kit that comprises:

(a) nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain; and

(b) a defined quantity of one or more nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or

central sensitization pain, for simultaneous, separate or sequential use in detecting and/or quantifying a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

IDENTIFICATION AND VALIDATION

[0081] Subtractive hybridization enables the identification of nucleic acid sequences whose expression profiles are modified by a stimulus. Upon stimulation of a system (in the case of this invention a nociceptive stimulus on an animal model) all observed changes in the level of nucleic acid sequence expression are due to the reaction of the system to the stimulus. Characterization of these changes in expression by way of identification of nucleic acid sequence and level of expression is both identification and validation.

[0082] The inventors have developed a four step process which allows for the simultaneous identification and validation of nucleic acid sequences whose expression are regulated by a pain stimulus, preferably a chronic pain stimulus, and more preferably a diabetic pain stimulus. This process may comprise the following steps:

- (a) induction of a nociceptive stimulus in test animals;
- (b) extraction of nucleic acids from specific neuronal tissue of test and control animals;
- (c) selective amplification of differentially expressed nucleic acid sequences; and
- (d) identification and characterization of differentially expressed gene products that are modulated by a nociceptive stimulus.

[0083] The above process is described in more detail below.

(a) Induction of nociceptive stimulus

[0084] The effect of the selected nociceptive stimulus on the test animal needs to be confirmable. The test subjects are therefore a species that has a "developed" nervous system, preferably similar to that of humans, most preferably rats or mice. Advantageously, the nociceptive stimulus is analogous to known pain paradigms in humans. One such paradigm of pain is the pain associated with diabetes, which can be induced in rodents with the use of streptozotocin (STZ). The present application requires the sequences to be down-regulated in two pain models which may be, but are not limited to models of neuropathic pain and/or central sensitization, and in which diabetic pain provides the first model and mechanical damage e.g. to a nerve leading into the spine can provide an appropriate second model.

[0085] Streptozotocin (STZ) induces hyperglycemia and Type 1 diabetes mellitus in rats. In particular, STZ contains a glucose analogue that allows it to be taken up by the glucose transporter 2 present on the surface of pancreatic β cells, the site of insulin synthesis. Once inside the cell, STZ causes a reduction in the level of nicotinamide adenine dinucleotide (NAD⁺). The decrease in NAD⁺ levels eventually leads to necrosis of the pancreatic β cell, causing a reduction in insulin levels and then diabetes, leading to neuropathy (diabetic) and neuropathic pain (R. B. Weiss, *Cancer Treat. Rep.*, **66**, 427-438 1982, Guy *et al*, *Diabetologica*, **28**, 131-137 1985; Ziegler *et al*, *Pain*, **34**, 1-10 1988; Archer *et al*, *J. Neural. Neurosurgeon. Psychiatry*, **46**, 491-499 1983). The diabetic rat model has been shown to be a reliable model of hyperalgesia. We have used an STZ-induced diabetic rat model to create a state of hyperalgesia that can be compared with control animals (Courteix *et al*, *Pain*, **53**, 81-88 1993).

[0086] Three models of neuropathic and/or central sensitization pain in rats, which involve nerve injury, may be used, see Ralston, DD (1998) Present models of neuropathic pain. *Pain Rev.* **5**: 83-100. The injuries are caused by (1) loosely tying four chromic gut sutures around the sciatic nerve (CCI model developed by Bennett, GJ and Y-K Xie, A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man, *Pain* **33**: 87-107 (1988), (2) tightly ligating one third to one half of the fibers in the sciatic nerve (model developed by Seltzer, Z, R Dubner, Y Shire, A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury, *Pain* **43**: 205-218, 1990), and (3) tightly ligating the dorsal spinal nerve of a rat at the L5 or L5 and L6 levels (L5 model developed by Kim, SH and JM Chung, An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, *Pain* **50**: 355-363, 1992).

(b) Extraction of nucleic acids from neuronal tissue of test and control animals

[0087] The inventors have determined that RNA extraction of whole spinal cord nervous tissue would provide a way of identifying nucleic acid sequences whose expression in spinal tissue is modulated by streptozotocin induced diabetes or by a mechanical nerve damage model for neuropathic and/or central sensitization pain e.g. CCI. Test (subjected to the nociceptive stimulus) and control animals were sacrificed, and the tissue to be studied e.g. neural tissue separated. Techniques for so doing vary widely from animal to animal and will be familiar to skilled persons.

[0088] A cDNA library can be prepared from total RNA extracted from neural tissue of the test and control animals. Where possible, however, it is preferred to isolate the mRNA from the total RNA of the test and control animals, by affinity chromatography on oligo (dT)-cellulose, and then reverse transcribe the mRNA from the test and control animals to give test and control cDNA. Converting mRNA from the test and control animals to corresponding cDNA may be carried out by any suitable reverse transcription method, e.g. a method as described by Gubler & Hoffman, *Gene*, 25, 263-269 (1983). If desired a proprietary kit may be used e.g. the CapFinder PCR cDNA Library Construction Kit (Life Technologies) which is based on long-distance PCR and permits the construction of cDNA libraries from nanograms of total RNA.

(c) Selective amplification of differentially expressed nucleic acids

[0089] The reverse transcribed cDNA of the test and control animals is subjected to subtractive hybridisation and amplification so that differentially expressed sequences become selectively amplified and commonly expressed sequences become suppressed, so as to over-produce DNA associated with said nociceptive stimulus. A wide range of subtractive hybridisation methods can be used, but the preferred method is so-called suppression subtractive hybridisation, see US-A-5565340 and Diatchenko *et al*, *Proc. Nat. Acad. Sci. USA*, 93, 6025-6030 (1996), the disclosures of which are herein incorporated by reference. Kits for carrying out this method are available from CLONTECH Laboratories, Inc.

(d) Cloning and Sequencing the differentially expressed cDNA

[0090] The differentially expressed cDNA is ligated into a cloning vector, after which cells of *E. coli* are transformed with the vector and cultured. Positive clones are selected and lysed to release plasmids containing the cDNA insert. The plasmids are primed using forward and reverse primers to either side of the cloning site and the cDNA insert is sequenced. Vector and adaptor sequences are then removed from the output data from the sequencer, leaving only the nucleotide sequence of the differentially expressed gene. The sequence is then checked against data held in a database for homology to known nucleotide sequences and genes, including expressed sequence tags (ESTs) and coding sequences for proteins.

(e) Validation of the above method

[0091] The importance of the sequences that we have identified in pain is confirmed by the fact that genes have been identified using this method that represent nucleic acid sequences which have previously been implicated in pain, including Calmodulin (pRCM1, Genebank X13933), Enkephalin (Genebank Y07503) and Neurotensin receptor type 2 (Genebank X97121).

[0092] The inventors have identified nucleic acid sequences of the MAP kinase pathway, a previously non pain-associated biological pathway. The inventors have subsequently shown that intra-spinal injection of a MEK inhibitor (MEK is part of the MAP kinase pathway) produces a powerful inhibition of pain (Patent application No US 60/144292). Subsequently, it has been shown that the MAP kinase is also implicated in acute inflammatory pain (Woolf *et al*, *Nature Neuroscience* 1999).

[0093] The invention will now be further described in the following Example.

EXAMPLE

Induction of diabetes

[0094] Diabetes was induced in adult (150-200g) male Sprague-Dawley rats (n=6) as described by Courteix *et al* (*supra*). Animals were injected intraperitoneally with streptozotocin (STZ)(50 mg/kg) dissolved in distilled water. Control or sham animals (age-matched animals, n=6) were injected with distilled water only.

Chronic Constrictive Injury (CCI)

[0095] Rats were anaesthetized with i.p. sodium phenobarbital, after which the common left sciatic nerve was exposed at the level of the middle of the thigh by blunt dissection through the biceps femoris and proximal to the sciatic trifurcation. Four ligatures (4.0 braided silk) were tied loosely around it with about 1mm spacing. The muscle was closed in layers and two wound clips were applied to close the skin incision. The wound was then covered with topical antibiotics.

Nociceptive testing

[0096] Static allodynia (a form of hyperalgesia) was measured using a method described by Chaplan *et al*, "Quantitative assessment of tactile allodynia in the rat paw", *J. Neurosci. Methods*, **53**, 55-63 (1994). A series of von Frey filaments of different buckling weight (i.e. the load required for the filament to bend) were applied to the plantar surface of the right hand paw. The starting filament had a buckling weight of 20g. Lifting of the paw was taken to be a positive result, in which case a filament with the next lowest buckling weight was used for the next measurement. The test was continued until a filament was found for which there was an absence of response for longer than 5 seconds whereas a re-test with the next heaviest filament gave a positive response. Animals were considered hyperalgesic if their thresholds were found to be <4g of those of comparable untreated rats, see Calcutt & Chaplan, "Spinal pharmacology of tactile allodynia in diabetic rats", *British J. Pharmacol*, **122**, 1478-1482 (1997).

Tissue Extraction

[0097] STZ-treated, CCI-treated and control animals were anaesthetized with 4% halothane and perfused with ice-cold 0.9% saline containing 1% citric acid (pH adjusted to 7.4 with NaOH). The animals were decapitated and the lumbar spinal cord exposed. A 2-centimetre length of spinal cord ending at L6 (lumbar-6 forward) was removed from the spinal column. Attached dorsal root ganglia and contaminating spinal connective tissues were removed. The spinal cord tissue was snap frozen in dry ice and isopentane. In the experiments that follow, procedures on the streptozocin-treated and control groups of animals are disclosed. It will be understood that for identification of CCI-treated animals the same experiments are performed, but using tissues from the CCI-treated animals and from control animals.

Total RNA Extraction

[0098] Total RNA was extracted from the pooled male rat tissues of the streptozocin-treated and control groups using the TRIZOL Reagent Kit (Life Technologies). Briefly, tissue samples were homogenised fully using a Polytron homogenizer in 1ml of TRIZOL reagent per 50-100mg of tissue. Homogenized samples were then incubated at room temperature for 5 minutes and phase separated using 0.2ml chloroform per 1ml TRIZOL reagent followed by centrifugation at 3,000g. The aqueous phase was transferred to a fresh tube and the RNA precipitated with an equal volume of isopropyl alcohol and followed by centrifugation at 10,000g. The RNA pellet was washed in 75% ethanol and re-centrifuged. The pellet was then air dried and re-suspended in water.

mRNA Extraction

[0099] In contrast to ribosomal RNA and transfer RNA, the vast majority of mRNAs of mammalian cells carry tracts of poly(A⁺) at their 3' termini. mRNAs can therefore be separated from the bulk of cellular RNA by affinity chromatography on oligo (dT)-cellulose. mRNA was extracted from Total RNA using the MESSAGEMAKER Kit (Life Technologies) in which mRNA (previously heated to 65°C in order to disrupt secondary structures and so expose the poly (A⁺) tails) was bound to oligo(dT) cellulose under high salt concentrations (0.5M NaCl) in a filter syringe. Unbound RNA was then washed away and the poly(A⁺) mRNA eluted in distilled water. A tenth of the volume of 7.5 M Ammonium Acetate, 50µg of glycogen/ml mRNA sample and 2 volumes of absolute alcohol were then added to the samples which were placed at -20°C overnight. Following precipitation, the mRNA was spun down at 12,000g for 30 minutes at 4°C. RNAase free water was used to re-suspend the pellets, which were then and stored at -80°C.

PCR SELECT

[0100] The technique used was based on that of the CLONTECH PCR Select Subtraction Kit. The following protocol was performed using STZ-treated lumbar spinal cord Poly A⁺ RNA as the 'Tester' and Sham lumbar spinal cord poly A⁺ RNA as the 'Driver' (Forward Subtraction). A second subtraction experiment using the Sham lumbar spinal cord mRNA as the 'Tester' and STZ treated lumbar spinal cord mRNA as the 'Driver' (Reverse Subtraction) was performed in parallel using the same reagents and protocol. As a control for both experiments, the subtraction was also carried out using human skeletal muscle mRNA that had been provided by the manufacturer.

First-Strand cDNA Synthesis

[0101] 2 µg of PolyA⁺ RNA and 1 µl of cDNA synthesis primer (10 µM) were combined in a 0.5ml Eppendorf tube and sterile H₂O was added where necessary to achieve a final volume of 5 µl. The contents were mixed gently and incubated in a thermal cycler at 70°C for 2 min. The tubes were then cooled on ice for two minutes, after which 2 µl of

5X First-strand buffer, 1 µl of dNTP mix (10 mM each), sterile H₂O and 1 µl of AMV reverse transcriptase (20 units/µl) was also added. The tubes were then placed at 42°C for 1.5 hr in an air incubator. First-strand cDNA synthesis was terminated by placing the tubes on ice. (the human skeletal muscle cDNA produced by this step was used as the 'control driver' in later steps).

Second-Strand cDNA Synthesis

[0102] 48.4 µl of Sterile H₂O, 16.0 µl of 5X Second-strand buffer, 1.6 µl of dNTP mix (10 mM) and 4.0 µl of 20X Second-strand enzyme cocktail were added to each of the first-strand synthesis reaction tubes. The contents were then mixed and incubated at 16°C in a thermal cycler for 2 hr. 6 units (2 µl) of T4 DNA polymerase was then introduced and the tubes were incubated for a further 30 min at 16°C. In order to terminate second-strand synthesis, 4 µl of 20X EDTA/glycogen mix was added. A phenol:chloroform extraction was then carried out using the following protocol:-

[0103] 100 µl of phenol:chloroform:isoamyl alcohol (25:24:1) was added to the tubes which were then vortexed thoroughly and centrifuged at 14,000 rpm for 10 min at room temperature. The top aqueous layer was removed and placed in a fresh tube. 100 µl of chloroform:isoamyl alcohol (24:1) was then added to the aqueous layer and the tubes were again vortexed and centrifuged at 14,000 rpm for 10 min. 40 µl of 4 M NH₄OAc and 300 µl of 95% ethanol were then added and the tubes centrifuged at 14,000 rpm for 20 min. The supernatant was removed carefully, then 500 µl of 80% ethanol was added to the pellet. The tubes were centrifuged at 14,000 rpm for 10 min and the supernatant was removed so that the pellet could be air-dried. The precipitate was then dissolved in 50 µl of H₂O. 6 µl was transferred to a fresh microcentrifuge tube. The remainder of the sample was stored at -20°C until needed.

Rsa I Digestion

[0104] All products of the above procedures were subjected to a restriction digest, using the restriction endonuclease *Rsa* I, in order to generate ds cDNA fragments that are short and thus are optimal for subtraction hybridisation due to the standard kinetics of the hybridisation. Also, as *Rsa* I makes a double stranded cut in the middle of a recognition sequence, 'blunt ends' of a known nucleotide sequence are produced allowing ligation of adaptors onto these ends in a later step. The following reagents were added to the 6 µl product of the second hybridisation (see above): 43.5 µl of ds cDNA, 5.0 µl 10X *Rsa* I restriction buffer and 1.5 µl of *Rsa* I (10 units/ µl). The reaction mixture was incubated at 37°C for 1.5 hr. 2.5 µl of 20X EDTA/glycogen mix was used to terminate the reaction. A phenol:chloroform extraction was then performed as above (second-strand cDNA synthesis section). The pellet produced was then dissolved in 5.5 µl of H₂O and stored at -20°C until needed. The preparation of the experimental 'Driver' cDNAs and the control skeletal muscle cDNA was thus completed.

Adaptor Ligation

[0105] The adaptors were not ligated to the driver cDNA.

[0106] 1 µl of each *Rsa* I-digested experimental cDNA (from the *Rsa* I Digestion above) was diluted with 5 µl of sterile water. Preparation of the control skeletal muscle tester cDNA was then undertaken by briefly centrifuging the tube containing control DNA (*Hae* III-digest of φX174 DNA [3 ng/ µl]) and diluting 2 µl of the DNA with 38 µl of sterile water (to 150 ng/ml). 1 µl of control skeletal muscle cDNA (from the *Rsa* I Digestion) was then mixed with 5 µl of the diluted φX174/ *Hae* III DNA (150 ng/ml) in order to produce the control skeletal muscle tester cDNA.

Preparation of the adaptor-ligated tester cDNA

[0107] A ligation master mix was prepared by combining 3 µl of sterile water, 2 µl of 5X ligation buffer and 1 µl T4 DNA ligase (400 units/µl) per reaction. 2 µl of adaptor 1 (10 µM) was then added to 2 µl of the diluted tester cDNA. To this, 6 µl of the ligation master mix was also added. The tube was therefore labeled Tester 1-1. In a separate tube, 2 µl of the adaptor 2R (10 µM) was mixed with 2 µl of the diluted tester cDNA and 6 µl of the master mix. This tube was named Tester 1-2.

[0108] 2 µl of Tester 1-1 and 2 µl of Tester 1-2 were then placed into fresh tubes. These would later be used as the unsubtracted tester control. The remainder of the contents of Tester 1-1 and Tester 1-2 tubes were then centrifuged briefly and incubated at 16°C overnight. The ligation reaction was stopped by adding 1 µl of EDTA/glycogen mix and the samples were heated at 72°C for 5 min in order to inactivate the ligase. In doing so, preparation of the experimental and control skeletal muscle adaptor-ligated tester cDNAs was complete.

[0109] 1 µl from each unsubtracted tester control was then removed and diluted into 1 ml of water. These samples were set aside as they were to be used later for PCR (see below). All of the samples were stored at -20°C

Analysis of Ligation efficiency

[0110] 1 µl of each ligated cDNA was diluted into 200 µl of water and the following reagents were then combined in four separate tubes:

Component	Tube:	1	2	3	4
Tester 1-1 (ligated to Adaptor 1)		1	1	-	-
Tester 1-2 (ligated to Adaptor 2R)		-	-	1	1
G3PDH 3' primer (10 µM)		1	1	1	1
G3PDH 5' primer (10 µM)		-	1	-	1
PCR primer 1 (10 µM)		1	-	1	-
Total volume µl		3	3	3	3

[0111] A master mix for all of the reaction tubes plus one additional tube was made up by adding 18.5 µl of sterile H₂O, 2.5 µl of 10X PCR reaction buffer, 0.5 µl of dNTP mix (10 mM), and 0.5 µl of 50X Advantage cDNA Polymerase Mix, per reaction, into a fresh tube. 22 µl of this master mix was then aliquotted into each of the 4 reaction tubes prepared above. The contents of the tubes were overlaid with 50 µl of mineral oil. The reaction mix was incubated in a thermal cycler at 75°C for 5 min in order to extend the adaptors. The following protocol was then carried out immediately in a thermal cycler (Perkin-Elmer GeneAmp PCR Systems 2400): 94°C for 30 sec (1 cycle), 94°C 10 sec, 65°C 30 sec and then 68°C 2.5 min (25 cycles)

First Hybridisation

[0112] 1.5 µl of the Adaptor 1-ligated Tester 1-1 was combined with 1.5 µl of the *Rsa* I-digested driver cDNA, prepared earlier and 1 µl of 4X Hybridisation buffer. This process was then repeated combining the Adaptor 2R-ligated Tester 1-2 with the *Rsa* I-digested driver cDNA and 4X hybridisation buffer. The samples were incubated in a thermal cycler at 98°C for 1.5 min followed by incubation at 68°C for 8 hr.

Second Hybridisation

[0113] 1 µl of Driver cDNA (i.e. the *Rsa* I-digested cDNA (see above)), 1 µl 4X Hybridisation buffer and 2 µl Sterile H₂O were all combined in a fresh tube. 1 µl of this mix was then removed and placed in a new tube, overlaid with 1 drop of mineral oil and incubated at 98°C for 1.5 min in order to denature the driver. The following procedure was used to simultaneously mix the driver with hybridisation samples 1 and 2 (prepared in the first hybridisation), thus ensuring that the two hybridisation samples were mixed together only in the presence of freshly denatured driver: A micropipettor was set at 15 µl. The pipette tip was then touched onto the mineral oil/sample interface of the tube containing hybridisation sample 2. The entire sample was drawn partway into the tip before it was removed from the tube in order to draw a small amount of air into the tip. The pipette tip was then touched onto the interface of the tube containing the freshly denatured driver (i.e. the tip contained both samples separated by a small pocket of air) before the entire mixture was transferred to the tube containing hybridisation sample 1. The reaction was then incubated at 68°C overnight. 200 µl of dilution buffer was added to the tube, which was then heated in a thermal cycler at 68°C for 7 min. The product of this second hybridisation was stored at -20°C.

PCR Amplification

[0114] Seven PCR reactions were set up: (1) The forward-subtracted experimental cDNA, (2) the unsubtracted tester control (see preparation of the adaptor ligated tester cDNA), (3) the reverse-subtracted experimental cDNA, (4) the unsubtracted tester control for the reverse subtraction, (5) the subtracted control skeletal muscle cDNA, (6) the unsubtracted tester control for the control subtraction, and (7) the PCR control subtracted cDNA (provided in the kit). The PCR control subtracted cDNA was required to provide a positive PCR control as it contained a successfully subtracted mixture of *Hae* III-digested ϕ X174 DNA.

[0115] The PCR templates were prepared by aliquotting 1 µl of each diluted cDNA (i.e., each subtracted sample from the second hybridisation and the corresponding diluted unsubtracted tester control produced by the adaptor ligation see above) into an appropriately labeled tube. 1 µl of the PCR control subtracted cDNA was placed into a fresh tube. A master mix for all of the primary PCR tubes, plus one additional reaction, was then prepared by combining 19.5 µl of sterile water, 2.5 µl of 10X PCR reaction buffer, 0.5 µl of dNTP Mix (10 mM), 1.0 µl of PCR primer 1 (10 µM)

and 0.5 µl of 50X Advantage cDNA Polymerase Mix. 24 µl of Master Mix was then aliquotted into each of the 7 reaction tubes prepared above and the mixture was overlaid with 50 µl of mineral oil, before being incubated in a thermal cycler at 75°C for 5 min in order to extend the adaptors. Thermal cycling was then immediately started using the following protocol: 94°C 25 sec (1 cycle), 94°C 10 sec, 66°C 30 sec and 72°C 1.5 min (32 cycles).

[0116] 3 µl of each primary PCR mixture was then diluted in 27 µl of H₂O, 1 µl of each of these dilutions was then placed into a fresh tube.

[0117] A master mix for the secondary PCRs, (plus an additional reaction) was set up by combining 18.5 µl of sterile water, 2.5 µl of 10X PCR reaction buffer, 1.0 µl of Nested PCR primer 1 (10 µM), 1.0 µl of Nested PCR primer 2R (10 µM), 0.5 µl of dNTP Mix (10 mM) and 0.5 µl of 50X Advantage cDNA Polymerase Mix per reaction. 24 µl of this Master Mix was then added into each reaction tube containing the 1 µl diluted primary PCR mixture. The following PCR protocol was then carried out: 94°C 10 sec, 68°C 30 sec and 72°C 1.5 min (12 cycles). The reaction products were then stored at -20°C.

Ligation into a Vector/ Transformation & PCR

[0118] The products of the PCR amplification (enriched for differentially expressed cDNAs) were ligated into the pCR2.1-TOPO vector using a T/A cloning kit (Invitrogen), transformed into TOPO One Shot competent cells according to the manufacturers protocol and grown up on LB (Luria-Bertani) Agar plates overnight at 37°C. 1,000 colonies were then individually picked (using fresh sterile tips) and dipped into 5 µl of sterile water which had been aliquotted previously into 96 well PCR plates. The water/colonies were heated in a thermal cycler at 100°C for 10 minutes in order to burst the cells, thus releasing the plasmids containing a differentially expressed cDNA insert. The 5 µl of water/plasmid was then used as a template in a PCR reaction (see below) using M13 Forward and Reverse primers (10 ng/µl), complementary to the M13 site present on either side of the cloning site on the vector. 5 µl of the PCR product was then run on a 2% agarose gel and stained by ethidium bromide. PCR products of an amplified insert were identified and 5 µl of the remainder of the PCR product (i.e. from the 15 µl that had not been run on the gel) was diluted 1/10 with water. 5 µl of the diluted PCR product was then used as a template in a sequencing reaction.

Sequencing

[0119] A sequencing reaction containing M13 primer (3.2 pmol/µl), 'BigDye' reaction mix (i.e. AmpliTaq® DNA polymerase, MgCl₂ buffer and fluorescent dNTPs [each of the four deoxynucleoside triphosphates is linked to a specific fluorescent donor dye which in turn is attached to a specific acceptor dye]) and cDNA template (diluted PCR product) was set up. The reaction was carried out on a thermal cycler for 25 cycles of 10 seconds at 96°C, 20 seconds at 50°C and 4 minutes at 60°C. Each reaction product was then purified through a hydrated Centri-Sep column, and lyophilised. The pellets were resuspended in Template Suppression Reagent and sequenced on an ABI Prism 310 Genetic Analyser. The analyser uses an ion laser to excite the specific donor dye that transfers its energy to the acceptor dye, which emits a specific energy spectrum that can be read by the sequencer.

[0120] The differentially expressed genes of the streptozocin-induced diabetes experiment and of the CCl experiment were sequenced at Parke-Davis, Cambridge and at the applicant's core sequencing facility in Ann Arbor, MI, USA.

Bioinformatics

[0121] The sequencing results were analysed using the computer program CHROMAS in which the vector and adaptor sequences were clipped off, leaving only the nucleotide sequence of the differentially expressed gene. Each sequence was then checked for homology to known genes, Expressed Sequence Tags (ESTs) and Proteins using various Basic Local Alignment Search Tool (BLAST) searches against the Genbank sequence database at the National Centre for Biotechnology Information, Bethesda, Maryland, USA (NCBI).

[0122] Lists were derived called STZup and STZdown and CClup and CCl down that contain the nucleic acid sequences from the forward and back subtracted libraries respectively. In each list there are given accession numbers and descriptions for the known rat genes identified, and where available corresponding mouse or human genes. Sequences that are considered to be of interest and that are down-regulated both in a streptozocin-induced diabetes model and in a chronic constrictive injury pain model are identified in Tables I - VI above and are listed below.

[0123] References have been given where available for the sequences that have been found, and sequence listings have been given in the form in which they currently appear in publicly searchable databases e.g. the NCBI database (National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Maryland, MD 20894, USA, www.ncbi.nlm.nih.gov). These sequence listings are given for the purposes of identification only. The invention includes the use of subsequently revised versions of the above sequences (which may incorporate small differences to the version set out herein) and homologous sequences or similar proteins in other species as

determined by a high percentage identity (e.g. above 50%, preferably above 90%), length of alignment and functional equivalence.

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SEQUENCE LISTING

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	Tyr Met Phe Trp Leu Leu Val Ser Tyr Glu Ser Pro Ala Lys His Pro	260	265	270
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	Leu Ile Ala Ala Leu Val His Tyr Gly Gly Val Ile Phe Tyr Ala Leu	485	490	495
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 35 40 45
 Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr
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 55 Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe
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	Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys	115	120	125
10	Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe	130	135	140
	Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn	145	150	155
15	Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser	165	170	175
	Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val	180	185	190
20	Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg	195	200	205
	Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp	210	215	220
25	Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val	225	230	235
	Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser	245	250	255
30	Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser	260	265	270
	Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys	275	280	285
35	Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu	290	295	300
	Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp	305	310	315
40	Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His	325	330	335
	Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg	340	345	350
45	Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp	355	360	365
	Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile	370	375	380
50	Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala	385	390	395
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	Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile 465 470 475 480		
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	Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys 500 505 510		
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	Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His 530 535 540		
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	Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp 565 570 575		
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	Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys 595 600 605		
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	Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu 625 630 635 640		
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	Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met 660 665 670		
45	Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys 675 680 685		
	Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile 690 695 700		
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	Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile 725 730 735		
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Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu
740 745 750

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755 760 765

Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly Val Leu
770 775 780

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785 790 795 800

Ser Asp Ala Ala Lys Pro Phe Ser Val Val Val Phe His Cys Arg His
805 810 815

15 Met Phe His Lys Glu Cys Leu Pro Met Pro Ser Met Asn Ser Ala Ala
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35 40 45

40 Lys His Leu Arg His Ser Ala Trp Pro Pro Thr Leu Leu Gln Met Val
50 55 60

His Thr Leu Ala Ser Asn Gly Ala Asn Ser Ile Trp Glu His Ser Leu
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45 Leu Asp Pro Ala Gln Val Gln Ser Gly Arg Arg Lys Ala Asn Pro Gln
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Asp Lys Val His Pro Ile Lys Ser Glu Phe Ile Arg Ala Lys Tyr Gln
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50 Met Leu Ala Phe Val His Lys Leu Pro Cys Arg Asp Asp Asp Gly Val
115 120 125

Thr Ala Lys Asp Leu Ser Lys Gln Leu His Ser Ser Val Arg Thr Gly
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55 Asn Leu Glu Thr Cys Leu Arg Leu Leu Ser Leu Gly Ala Gln Ala Asn

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	Pro Gly Ser Pro Asp Val Asn Gly Arg Thr Pro Ile Asp Tyr Ala Arg						
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	Glu Leu Thr Asp Arg Leu Ala Phe Tyr Leu Cys Gly Arg Lys Pro Asp						
		225		230		235	
15	His Lys Asn Gly His Tyr Ile Ile Pro Gln Met Ala Asp Arg Ser Arg						
		245		250		255	
	Gln Lys Cys Met Ser Gln Ser Leu Asp Leu Ser Glu Leu Ala Lys Ala						
		260		265		270	
20	Ala Lys Lys Lys Leu Gln Ala Leu Ser Asn Arg Leu Phe Glu Glu Leu						
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	Ala Met Asp Val Tyr Asp Glu Val Asp Arg Arg Glu Asn Asp Ala Val						
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25	Trp Leu Ala Thr Gln Asn His Ser Thr Leu Val Thr Glu Arg Ser Ala						
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<220>
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Lys Leu Pro Phe Gln Arg Leu Val Arg Glu Ile Ala Gln Asp Phe Lys
65 70 75 80
Thr Asp Leu Arg Phe Gln Ser Ala Ala Ile Gly Ala Leu Gln Glu Ala
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Ser Glu Ala Tyr Leu Val Gly Leu Phe Glu Asp Thr Asn Leu Cys Ala
100 105 110
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 50 Ala Val Asn Glu Phe Val Glu Gln Leu Lys Gln Glu Gly Val Phe Ala
 660 665 670
 Lys Glu Val Arg Thr Gly Gly Leu Ala Phe His Ser Tyr Phe Met Glu
 675 680 685
 55 Gly Ile Ala Pro Thr Leu Leu Gln Ala Leu Lys Lys Val Ile Arg Glu

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	690	695	700
5	Pro Arg Pro Arg Ser Ala Arg Trp Leu Ser Thr Ser Ile Pro Glu Ala 705 710 715 720		
	Gln Trp Gln Ser Ser Leu Ala Arg Thr Ser Ser Ala Glu Tyr Asn Val 725 730 735		
10	Asn Asn Leu Val Ser Pro Val Leu Phe Gln Glu Ala Leu Trp His Val 740 745 750		
	Pro Glu His Ala Val Val Leu Glu Ile Ala Pro His Ala Leu Leu Gln 755 760 765		
15	Ala Val Leu Lys Arg Gly Val Lys Pro Ser Cys Thr Ile Ile Pro Leu 770 775 780		
	Met Lys Arg Asp His Lys Asp Asn Leu Glu Phe Phe Leu Thr Asn Leu 785 790 795 800		
20	Gly Lys Val His Leu Thr Gly Ile Asp Ile Asn Pro Asn Ala Leu Phe 805 810 815		
	Pro Pro Val Glu Phe Pro Val Pro Arg Gly Thr Pro Leu Ile Ser Pro 820 825 830		
25	His Ile Lys Trp Asp His Ser Gln Thr Trp Asp Ile Pro Val Ala Glu 835 840 845		
	Asp Phe Pro Asn Gly Ser Ser Ser Ser Ser Ala Thr Val Tyr Asn Ile 850 855 860		
30	Asp Ala Ser Ser Glu Ser Ser Asp His Tyr Leu Val Asp His Cys Ile 865 870 875 880		
	Asp Gly Arg Val Leu Phe Pro Gly Thr Gly Tyr Leu Tyr Leu Val Trp 885 890 895		
35	Lys Thr Leu Ala Arg Ser Leu Ser Leu Ser Leu Glu Glu Thr Pro Val 900 905 910		
	Val Phe Glu Asn Val Thr Phe His Gln Ala Thr Ile Leu Pro Arg Thr 915 920 925		
40	Gly Thr Val Pro Leu Glu Val Arg Leu Leu Glu Ala Ser His Ala Phe 930 935 940		
	Glu Val Ser Asp Ser Gly Asn Leu Ile Val Ser Gly Lys Val Tyr Gln 945 950 955 960		
45	Trp Glu Asp Pro Asp Ser Lys Leu Phe Asp His Pro Glu Val Pro Ile 965 970 975		
	Pro Ala Glu Ser Glu Ser Val Ser Arg Leu Thr Gln Gly Glu Val Tyr 980 985 990		
50	Lys Glu Leu Arg Leu Arg Gly Tyr Asp Tyr Gly Pro His Phe Gln Gly 995 1000 1005		
	Val Tyr Glu Ala Thr Leu Glu Gly Glu Gln Gly Lys Leu Leu Trp Lys 1010 1015 1020		
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	Asp Asn Trp Val Thr Phe Met Asp Thr Met Leu Gln Ile Ser Ile Leu	
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	Tyr Ile Asp Pro Ala Thr His Leu Gln Lys Val Tyr Met Leu Glu Gly	
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10	Asp Thr Gln Val Ala Asp Val Thr Thr Ser Arg Cys Leu Gly Val Thr	
		1075 1080 1085
	Val Ser Gly Gly Val Tyr Ile Ser Arg Leu Gln Thr Thr Ala Thr Ser	
		1090 1095 1100
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	Thr Pro His Val Glu Pro Glu Cys Leu Ser Glu Ser Ala Ile Leu Gln	
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20	Lys Glu Leu Gln Leu Cys Lys Gly Leu Ala Lys Ala Leu Gln Thr Lys	
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	Ala Thr Gln Gln Gly Leu Lys Met Thr Val Pro Gly Leu Glu Asp Leu	
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	Gln Ala Leu Lys Ala Cys Ile Asp Thr Ala Leu Glu Asn Leu Ser Thr	
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35	Leu Lys Met Lys Val Val Glu Val Leu Ala Gly Glu Gly His Leu Tyr	
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	Ser His Ile Ser Ala Leu Leu Asn Thr Gln Pro Met Leu Gln Leu Glu	
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	Lys Leu Gln Gln His Asp Val Ala Gln Gly Gln Trp Asp Pro Ser Gly	
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	Ala Leu Ala Thr Leu Gly Asp Pro Ala Leu Ala Leu Asp Asn Met Val	
		1315 1320 1325
50	Ala Ala Leu Lys Asp Gly Gly Phe Leu Leu Met His Thr Val Leu Lys	
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55	Gly His Ala Leu Gly Glu Thr Leu Ala Cys Leu Pro Ser Glu Val Gln	
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Pro Gly Pro Ser Phe Leu Ser Gln Glu Glu Trp Glu Ser Leu Phe Ser
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5 Arg Lys Ala Leu His Leu Val Gly Leu Lys Lys Ser Phe Tyr Gly Thr
1380 1385 1390

Ala Leu Phe Leu Cys Arg Arg Leu Ser Pro Gln Asp Lys Pro Ile Phe
1395 1400 1405

10 Leu Pro Val Glu Asp Thr Ser Phe Gln Trp Val Asp Ser Leu Lys Ser
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Ile Leu Ala Thr Ser Ser Ser Gln Pro Val Trp Leu Thr Ala Met Asn
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15 Cys Pro Thr Ser Gly Val Val Gly Leu Val Asn Cys Leu Arg Lys Glu
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Pro Gly Gly His Arg Ile Arg Cys Ile Leu Leu Ser Asn Leu Ser Ser
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20 Thr Ser His Val Pro Lys Leu Asp Pro Gly Ser Ser Glu Leu Gln Lys
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Val Leu Glu Ser Asp Leu Val Met Asn Val Tyr Arg Asp Gly Ala Trp
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25 Gly Ala Phe Arg His Phe Gln Leu Glu Gln Asp Lys Pro Glu Glu Gln
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Thr Ala His Ala Phe Val Asn Val Leu Thr Arg Gly Asp Leu Ala Ser
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30 Ile Arg Trp Val Ser Ser Pro Leu Lys His Met Gln Pro Pro Ser Ser
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Ser Gly Ala Gln Leu Cys Thr Val Tyr Tyr Ala Ser Leu Asn Phe Arg
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35 Asp Ile Met Leu Ala Thr Gly Lys Leu Ser Pro Asp Ala Ile Pro Gly
1570 1575 1580

Lys Trp Ala Ser Arg Asp Cys Met Leu Gly Met Glu Phe Ser Gly Arg
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40 Asp Lys Cys Gly Arg Arg Val Met Gly Leu Val Pro Ala Glu Gly Leu
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Ala Thr Ser Val Leu Leu Ser Pro Asp Phe Leu Trp Asp Val Pro Ser
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45 Ser Trp Thr Leu Glu Glu Ala Ala Ser Val Pro Val Val Tyr Thr Thr
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50 Ala Tyr Tyr Ser Leu Val Val Arg Gly Arg Ile Gln His Gly Glu Thr
1650 1655 1660

Val Leu Ile His Ser Gly Ser Gly Gly Val Gly Gln Ala Ala Ile Ser
1665 1670 1675 1680

55 Ile Ala Leu Ser Leu Gly Cys Arg Val Phe Thr Thr Val Gly Ser Ala

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	Ser Phe Ala Asn Ser Arg Asp Thr Ser Phe Glu Gln His Val Leu Leu 1715	1720	1725
10	His Thr Gly Gly Lys Gly Val Asp Leu Val Leu Asn Ser Leu Ala Glu 1730	1735	1740
	Glu Lys Leu Gln Ala Ser Val Arg Cys Leu Ala Gln His Gly Arg Phe 1745	1750	1755
15	Leu Glu Ile Gly Lys Phe Asp Leu Ser Asn Asn His Pro Leu Gly Met 1765	1770	1775
	Ala Ile Phe Leu Lys Asn Val Thr Phe His Gly Ile Leu Leu Asp Ala 1780	1785	1790
20	Leu Phe Glu Gly Ala Asn Asp Ser Trp Arg Glu Val Ala Glu Leu Leu 1795	1800	1805
	Lys Ala Gly Ile Arg Asp Gly Val Val Lys Pro Leu Lys Cys Thr Val 1810	1815	1820
25	Phe Pro Lys Ala Gln Val Glu Asp Ala Phe Arg Tyr Met Ala Gln Gly 1825	1830	1835
	Lys His Ile Gly Lys Val Leu Val Gln Val Arg Glu Glu Glu Pro Glu 1845	1850	1855
30	Ala Met Leu Pro Gly Ala Gln Pro Thr Leu Ile Ser Ala Ile Ser Lys 1860	1865	1870
	Thr Phe Cys Pro Glu His Lys Ser Tyr Ile Ile Thr Gly Gly Leu Gly 1875	1880	1885
35	Gly Phe Gly Leu Glu Leu Ala Arg Trp Leu Val Leu Arg Gly Ala Gln 1890	1895	1900
	Arg Leu Val Leu Thr Ser Arg Ser Gly Ile Arg Thr Gly Tyr Gln Ala 1905	1910	1915
40	Lys His Val Arg Glu Trp Arg Arg Gln Gly Ile His Val Leu Val Ser 1925	1930	1935
	Thr Ser Asn Val Ser Ser Leu Glu Gly Ala Arg Ala Leu Ile Ala Glu 1940	1945	1950
45	Ala Thr Lys Leu Gly Pro Val Gly Gly Val Phe Asn Leu Ala Met Val 1955	1960	1965
	Leu Arg Asp Ala Met Leu Glu Asn Gln Thr Pro Glu Leu Phe Gln Asp 1970	1975	1980
50	Val Asn Lys Pro Lys Tyr Asn Gly Thr Leu Asn Leu Asp Arg Ala Thr 1985	1990	1995
	Arg Glu Ala Cys Pro Glu Leu Asp Tyr Phe Val Ala Phe Ser Ser Val 2005	2010	2015
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Ser Cys Gly Arg Gly Asn Ala Gly Gln Ser Asn Tyr Gly Phe Ala Asn
2020 2025 2030

5 Ser Thr Met Glu Arg Ile Cys Glu Gln Arg Arg His Asp Gly Leu Pro
2035 2040 2045

Gly Leu Ala Val Gln Trp Gly Ala Ile Gly Asp Val Gly Ile Ile Leu
2050 2055 2060

10 Glu Ala Met Gly Thr Asn Asp Thr Val Val Gly Gly Thr Leu Pro Gln
2065 2070 2075 2080

Arg Ile Ser Ser Cys Met Glu Val Leu Asp Leu Phe Leu Asn Gln Pro
2085 2090 2095

15 His Ala Val Leu Ser Ser Phe Val Leu Ala Glu Lys Lys Ala Val Ala
2100 2105 2110

His Gly Asp Gly Glu Ala Gln Arg Asp Leu Val Lys Ala Val Ala His
2115 2120 2125

20 Ile Leu Gly Ile Arg Asp Leu Ala Gly Ile Asn Leu Asp Ser Ser Leu
2130 2135 2140

Ala Asp Leu Gly Leu Asp Ser Leu Met Gly Val Glu Val Arg Gln Ile
2145 2150 2155 2160

25 Leu Glu Arg Glu His Asp Leu Val Leu Pro Ile Arg Glu Val Arg Gln
2165 2170 2175

Leu Thr Leu Arg Lys Leu Gln Glu Met Ser Ser Lys Ala Gly Ser Asp
2180 2185 2190

30 Thr Glu Leu Ala Ala Pro Lys Ser Lys Asn Asp Thr Ser Leu Lys Gln
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Ala Gln Leu Asn Leu Ser Ile Leu Leu Val Asn Pro Glu Gly Pro Thr
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35 Leu Thr Arg Leu Asn Ser Val Gln Ser Ser Glu Arg Pro Leu Phe Leu
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Val His Pro Ile Glu Gly Ser Ile Thr Val Phe His Ser Leu Ala Ala
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40 Lys Leu Ser Val Pro Thr Tyr Gly Leu Gln Cys Thr Gln Ala Ala Pro
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2275 2280 2285

45 Gln Val Gln Pro Glu Gly Pro Tyr Arg Val Ala Gly Tyr Ser Phe Gly
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2305 2310 2315 2320

50 Pro Ala Pro Ala His Asn Asn Leu Phe Leu Phe Asp Gly Ser His Thr
2325 2330 2335

55 Tyr Val Leu Ala Tyr Thr Gln Ser Tyr Arg Ala Lys Leu Thr Pro Gly
2340 2345 2350

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Cys Glu Ala Glu Ala Glu Ala Glu Ala Ile Cys Phe Phe Ile Lys Gln
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 5 Phe Val Asp Ala Glu His Ser Lys Val Leu Glu Ala Leu Leu Pro Leu
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 2385 2390 2395 2400
 10 Ser His Gln Ser Leu Asp Arg Arg Asp Leu Ser Phe Ala Ala Val Ser
 2405 2410 2415
 Phe Tyr Tyr Lys Leu Arg Ala Ala Asp Gln Tyr Lys Pro Lys Ala Lys
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 15 Tyr His Gly Asn Val Ile Leu Leu Arg Ala Lys Thr Gly Gly Thr Tyr
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<223> Aldose reductase

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35 40 45
Tyr Gln Asn Glu Lys Glu Val Gly Val Ala Leu Gln Glu Lys Leu Lys
25 50 55 60
Glu Gln Val Val Lys Arg Gln Asp Leu Phe Ile Val Ser Lys Leu Trp
65 70 75 80
Cys Thr Phe His Asp Gln Ser Met Val Lys Gly Ala Cys Gln Lys Thr
30 85 90 95
Leu Ser Asp Leu Gln Leu Asp Tyr Leu Asp Leu Tyr Leu Ile His Trp
100 105 110
Pro Thr Gly Phe Lys Pro Gly Pro Asp Tyr Phe Pro Leu Asp Ala Ser
35 115 120 125
Gly Asn Val Ile Pro Ser Asp Thr Asp Phe Val Asp Thr Trp Thr Ala
130 135 140
Met Glu Gln Leu Val Asp Glu Gly Leu Val Lys Ala Ile Gly Val Ser
40 145 150 155 160
Asn Phe Asn Pro Leu Gln Ile Glu Arg Ile Leu Asn Lys Pro Gly Leu
165 170 175
Lys Tyr Lys Pro Ala Val Asn Gln Ile Glu Cys His Pro Tyr Leu Thr
45 180 185 190
Gln Glu Lys Leu Ile Glu Tyr Cys His Cys Lys Gly Ile Val Val Thr
195 200 205
Ala Tyr Ser Pro Leu Gly Ser Pro Asp Arg Pro Trp Ala Lys Pro Glu
50 210 215 220
Asp Pro Ser Leu Leu Glu Asp Pro Arg Ile Lys Glu Ile Ala Ala Lys
55 225 230 235 240

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Tyr Asn Lys Thr Thr Ala Gln Val Leu Ile Arg Phe Pro Ile Gln Arg
 245 250 255
 5 Asn Leu Val Val Ile Pro Lys Ser Val Thr Pro Ala Arg Ile Ala Glu
 260 265 270
 Asn Phe Lys Val Phe Asp Phe Glu Leu Ser Asn Glu Asp Met Ala Thr
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 5 Leu Pro Gly Phe Gly Ile Ile Ser His Val Val Thr Tyr Tyr Ser Gly
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 50 55 60
 10 Ile Gly Phe Leu Gly Phe Ile Val Trp Ala His His Met Phe Thr Val
 65 70 75 80
 Gly Leu Asp Val Asp Thr Arg Ala Tyr Phe Thr Ser Ala Thr Met Ile
 85 90 95
 15 Ile Ala Ile Pro Thr Gly Val Lys Val Phe Ser Trp Leu Ala Thr Leu
 100 105 110
 His Gly Gly Asn Ile Lys Trp Ser Pro Ala Met Leu Trp Ala Leu Gly
 115 120 125
 20 Phe Ile Phe Leu Phe Thr Val Gly Gly Leu Thr Gly Ile Val Leu Ser
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 25 His Phe His Tyr Val Leu Ser Met Gly Ala Val Phe Ala Ile Met Ala
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 Cys Phe Val His Trp Phe Pro Leu Phe Ser Gly Tyr Thr Leu Asn Asp
 180 185 190
 30 Thr Trp Ala Lys Ala His Phe Ala Ile Met Phe Val Gly Val Asn Met
 195 200 205
 Thr Phe Phe Pro Gln His Phe Leu Gly Leu Ala Gly Met Pro Arg Arg
 210 215 220
 35 Tyr Ser Asp Tyr Pro Asp Ala Tyr Thr Thr Trp Asn Thr Val Ser Ser
 225 230 235 240
 Met Gly Ser Phe Ile Ser Leu Thr Ala Val Leu Val Met Ile Phe Met
 245 250 255
 40 Ile Trp Glu Ala Phe Ala Ser Lys Arg Glu Val Leu Ser Ile Ser Tyr
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 35 40 45
 Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met
 50 55 60
 40 Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala
 65 70 75 80
 Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
 85 90 95
 45 Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
 100 105 110
 Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
 115 120 125
 50 Ser Pro Asp Cys Thr Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu
 130 135 140
 Thr Tyr Val Thr Trp Lys Leu Ser Gly Leu Pro Lys His Arg Val Ile
 145 150 155 160
 55 Gly Ser Gly Cys Asn Leu Asp Ser Ala Arg Phe Arg Tyr Leu Met Ala

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	Gly Val Ser Leu Gln Glu Leu Asn Pro Glu Met Gly Thr Asp Asn Asp		
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	Ser Glu Asn Trp Lys Glu Val His Lys Met Val Val Asp Ser Ala Tyr		
	225	230	235
	Glu Val Ile Lys Leu Lys Gly Tyr Thr Asn Trp Ala Ile Gly Leu Ser		
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	Val Ala Asp Leu Ile Glu Ser Met Leu Lys Asn Leu Ser Arg Ile His		
	260	265	270
	Pro Val Ser Thr Met Val Lys Gly Met Tyr Gly Ile Glu Asn Glu Val		
20	275	280	285
	Phe Leu Ser Leu Pro Cys Ile Leu Asn Ala Arg Gly Leu Thr Ser Val		
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	Ile Asn Gln Lys Leu Lys Asp Asp Glu Val Ala Gln Leu Arg Lys Ser		
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1217

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 <213> Homo sapiens

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 35 40 45
 Gly Asp Ile Ser Val Cys Glu Trp Tyr Gln Arg Val Tyr Gln Ser Leu
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 Thr Phe Pro Gly Lys Ile
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 agactagaaa ctgctggcag aactacctgg acttccaccg ctgtcagaag gcaatgaccg 180
 ctaaaggagg cgatatctct gtgtgcgaat ggtaccagcg tgtgtaccag tccctctgcc 240
 ccacatcctg ggtcacagac tgggatgagc aacgggctga aggcacgttt cccgggaaga 300
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 aaaactcatt ggaaaagtg 439

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 <212> PRT
 <213> Homo sapiens

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 5 Gly Ala Gln Cys Asp Lys Pro Asn Lys Glu Phe Met Leu Cys Arg Trp
 35 40 45
 Glu Glu Lys Asp Pro Arg Arg Cys Leu Glu Glu Gly Lys Leu Val Asn
 50 55 60
 10 Lys Cys Ala Leu Asp Phe Phe Arg Gln Ile Lys Arg His Cys Ala Glu
 65 70 75 80
 Pro Phe Thr Glu Tyr Trp Thr Cys Ile Asp Tyr Thr Gly Gln Gln Leu
 85 90 95
 15 Phe Arg His Cys Arg Lys Gln Gln Ala Lys Phe Asp Glu Cys Val Leu
 100 105 110
 Asp Lys Leu Gly Trp Val Arg Pro Asp Leu Gly Glu Leu Ser Lys Val
 115 120 125
 20 Thr Lys Val Lys Thr Asp Arg Pro Leu Pro Glu Asn Pro Tyr His Ser
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 Arg Pro Arg Pro Asp Pro Ser Pro Glu Ile Glu Gly Asp Leu Gln Pro
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 25 Ala Thr His Gly Ser Arg Phe Tyr Phe Trp Thr Lys
 165 170

30 <210> 37
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35 <220>
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 gaaaattagt tctgctgtgc ttaaagctgc ggcccatcac tatggagctc aatgtgataa 180
 gccaacaag gaatttatgc lctgccgctg ggaagagaaa gatccgaggc ggtgtttaga 240
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 tcaactgtcg aaacagcagg caaagtttga cgagtgtgtg ctggacaaac tgggctgggt 420
 gcggcctgac ctgggagaac tgtcaaaggt caccaaagtg aaaacagatc gacctttacc 480
 45 ggagaatccc tatcactcaa gaccaagacc ggatcccagc cctgagatcg agggagatct 540
 gcagcctgcc acacatggca gccgctttta tttctggacc aagtaaagat ggggtcgtgg 600
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55 <220>
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 35 40 45
 His Phe Tyr Asp Thr Val Lys Gly Ser Asp Trp Leu Gly Asp Gln Asp
 50 55 60
 15 Ala Ile His Tyr Met Thr Glu Gln Ala Pro Ala Ser Val Val Glu Leu
 65 70 75 80
 Glu Asn Tyr Gly Met Pro Phe Ser Arg Thr Glu Asp Gly Lys Ile Tyr
 85 90 95
 20 Gln Arg Ala Phe Gly Gly Gln Ser Leu Lys Phe Gly Lys Gly Gly Gln
 100 105 110
 Ala His Arg Cys Cys Cys Val Ala Asp Arg Thr Gly His Ser Leu Leu
 115 120 125
 25 His Thr Leu Tyr Gly Arg Ser Leu Arg Tyr Asp Thr Ser Tyr Phe Val
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 Glu Tyr Phe Ala Leu Asp Leu Leu Met Glu Asn Gly Glu Cys Arg Gly
 145 150 155 160
 30 Val Ile Ala Leu Cys Ile Glu Asp Gly Ser Ile His Arg Ile Arg Ala
 165 170 175
 Lys Asn Thr Val Ile Ala Thr Gly Gly Tyr Gly Arg Thr Tyr Phe Ser
 180 185 190
 35 Cys Thr Ser Ala His Thr Ser Thr Gly Asp Gly Thr Ala Met Val Thr
 195 200 205
 Arg Ala Gly Leu Pro Cys Gln Asp Leu Glu Phe Val Gln Phe His Pro
 210 215 220
 40 Thr Gly Ile Tyr Gly Ala Gly Cys Leu Ile Thr Glu Gly Cys Arg Gly
 225 230 235 240
 Glu Gly Gly Ile Leu Ile Asn Ser Gln Gly Glu Arg Phe Met Glu Arg
 245 250 255
 45 Tyr Ala Pro Val Ala Lys Asp Leu Ala Ser Arg Asp Val Val Ser Arg
 260 265 270
 Ser Met Thr Leu Glu Ile Arg Glu Gly Arg Gly Cys Gly Pro Glu Lys
 275 280 285
 50 Asp His Val Tyr Leu Gln Leu His His Leu Pro Pro Glu Gln Leu Ala
 290 295 300
 Thr Arg Leu Pro Gly Ile Ser Glu Thr Ala Met Ile Phe Ala Gly Val
 305 310 315 320
 55

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Asp Val Thr Lys Glu Pro Ile Pro Val Leu Pro Thr Val His Tyr Asn
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 5 Met Gly Gly Ile Pro Thr Asn Tyr Lys Gly Gln Val Leu Lys His Val
 340 345 350
 Asn Gly Gln Asp Gln Ile Val Pro Gly Leu Tyr Ala Cys Gly Glu Ala
 355 360 365
 10 Ala Cys Ala Ser Val His Gly Ala Asn Arg Leu Gly Ala Asn Ser Leu
 370 375 380
 Leu Asp Leu Val Val Phe Gly Arg Ala Cys Ala Leu Ser Ile Ala Glu
 385 390 395 400
 15 Ser Cys Arg Pro Gly Asp Lys Val Pro Ser Ile Lys Ala Asn Ala Gly
 405 410 415
 Glu Glu Ser Val Met Asn Leu Asp Lys Leu Arg Phe Ala Asp Gly Ser
 420 425 430
 20 Ile Arg Thr Ser Glu Leu Arg Leu Asn Met Gln Lys Ser Met Gln Asn
 435 440 445
 His Ala Ala Val Phe Arg Val Gly Ser Val Leu Gln Glu Gly Cys Glu
 450 455 460
 25 Lys Ile Ser Gln Leu Tyr Gly Asp Leu Lys His Leu Lys Thr Phe Asp
 465 470 475 480
 Arg Gly Met Val Trp Asn Thr Asp Leu Val Glu Thr Leu Glu Leu Gln
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      <213> Homo sapiens

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          35             40             45
35     Ile Ala Ser Leu Glu Asn Tyr Ser Pro Val Ser Arg Ile Gly Leu Phe
          50             55             60
      Ile Lys Ala Gly Ser Arg Tyr Glu Asp Phe Ser Asn Leu Gly Thr Thr
          65             70             75             80
40     His Leu Leu Arg Leu Thr Ser Ser Leu Thr Thr Lys Gly Ala Ser Ser
          85             90             95
      Phe Lys Ile Thr Arg Gly Ile Glu Ala Val Gly Gly Lys Leu Ser Val
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45     Thr Ala Thr Arg Glu Asn Met Ala Tyr Thr Val Glu Cys Leu Arg Gly
          115            120            125
      Asp Val Asp Ile Leu Met Glu Phe Leu Leu Asn Val Thr Thr Ala Pro
          130            135            140
50     Glu Phe Arg Arg Trp Glu Val Ala Asp Leu Gln Pro Gln Leu Lys Ile
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      Asp Lys Ala Val Ala Phe Gln Asn Pro Gln Thr His Val Ile Glu Asn
          165            170            175
55

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His Leu Gly Val Gln Val Lys Gly Glu Asp Glu Glu Asp Asn Asn Leu
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Glu Val Arg Glu Thr Lys Met Lys Gly Lys Ser Gly Arg Phe Phe Thr
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Val Lys Leu Pro Val Ala Leu Asp Pro Gly Ser Lys Ile Ser Ile Val
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<211> 284

<212> PRT

<213> Rattus norvegicus

<220>

<223> Sulfotransferase-like protein

<400> 46

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Met Gly Lys Cys Asp Leu Thr Phe Asp Phe Tyr Leu
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<210> 47

<211> 2239

<212> DNA

<213> Rattus norvegicus

<220>

<223> Sulfotransferase-like protein

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<210> 48

<211> 235

<212> PRT

<213> Rattus norvegicus

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<220>

<223> F1-ATPase alpha subunit

<400> 48

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Arg Ala Ala Lys Met Asn Asp Ser Phe Gly Gly Gly Ser Leu Thr Ala
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Leu Pro Val Ile Glu Thr Gln Ala Gly Asp Val Ser Ala Tyr Ile Pro
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Thr Asn Val Ile Ser Ile Thr Asp Gly Gln Ile Phe Leu Glu Thr Glu
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Leu Phe Tyr Lys Gly Ile Arg Pro Ala Ile Asn Val Gly Leu Ser Val
85 90 95

Ser Arg Val Gly Ser Ala Ala Gln Thr Arg Ala Met Lys Gln Val Ala
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Gly Thr Met Lys Leu Glu Leu Ala Gln Tyr Arg Glu Val Ala Ala Phe
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Phe Leu Ser His Val Val Ser Gln His Gln Ser Leu Leu Gly Asn Ile
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<211> 1066

<212> DNA

<213> Rattus norvegicus

<220>

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<210> 50
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 <212> PRT
 <213> Rattus norvegicus

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 <223> F1F0 ATPase delta subunit

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Ala Gly Pro Gly Gln Met Ser Phe Thr Phe Ala Ser Pro Thr Gln Val
 35 40 45

Phe Phe Asp Gly Ala Asn Val Arg Gln Val Asp Val Pro Thr Leu Thr
 50 55 60

35

Gly Ala Phe Gly Ile Leu Ala Ser His Val Pro Thr Leu Gln Val Leu
 65 70 75 80

Arg Pro Gly Leu Val Met Val His Ala Glu Asp Gly Thr Thr Thr Lys
 85 90 95

40

Tyr Phe Val Ser Ser Gly Ser Val Thr Val Asn Ala Asp Ser Ser Val
 100 105 110

Gln Leu Leu Ala Glu Glu Val Val Thr Leu Asp Met Leu Asp Leu Gly
 115 120 125

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Ala Ala Arg Ala Asn Leu Glu Lys Ala Gln Ser Glu Leu Ser Gly Ala
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Ala Asp Glu Ala Ala Arg Ala Glu Ile Gln Ile Arg Ile Glu Ala Asn
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Glu Ala Leu Val Lys Ala Leu Glu
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<210> 51
 <211> 811

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<212> DNA
<213> Rattus norvegicus

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<223> F1F0 ATPase delta subunit

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<210> 52
<211> 572
<212> PRT
<213> Homo sapiens

<220>
<223> Dihydropyrimidinase-related protein

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35 40 45
Leu Ile Val Pro Gly Gly Val Lys Thr Ile Glu Ala His Ser Arg Met
50 55 60
Val Ile Pro Gly Gly Ile Asp Val His Thr Arg Phe Gln Met Pro Asp
65 70 75 80
Gln Gly Met Thr Ser Ala Asp Asp Phe Phe Gln Gly Thr Lys Ala Ala
85 90 95
Leu Ala Gly Gly Thr Thr Met Ile Ile Asp His Val Val Pro Glu Pro
100 105 110
Gly Thr Ser Leu Leu Ala Ala Phe Asp Gln Trp Arg Glu Trp Ala Asp
115 120 125
Ser Lys Ser Cys Cys Asp Tyr Ser Leu His Val Asp Ile Ser Glu Trp
130 135 140
His Lys Gly Ile Gln Glu Glu Met Glu Ala Leu Val Lys Asp His Gly
145 150 155 160

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<212> DNA
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<223> Dihydropyrimidinase-related protein

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<220>
<223> MAG

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<400> 59

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10 Glu Leu Arg Pro Ala Val Val His Gly Val Trp Tyr Phe Asn Ser Pro
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Tyr Pro Lys Asn Tyr Pro Pro Val Val Phe Lys Ser Arg Thr Gln Val
65 70 75 80

15 Val His Glu Ser Phe Gln Gly Arg Ser Arg Leu Leu Gly Asp Leu Gly
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Leu Arg Asn Cys Thr Leu Leu Leu Ser Thr Leu Ser Pro Glu Leu Gly
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20 Gly Lys Tyr Tyr Phe Arg Gly Asp Leu Gly Gly Tyr Asn Gln Tyr Thr
115 120 125

Phe Ser Glu His Ser Val Leu Asp Ile Ile Asn Thr Pro Asn Ile Val
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25 Val Pro Pro Glu Val Val Ala Gly Thr Glu Val Glu Val Ser Cys Met
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30 His Glu Gly Leu Gly Glu Pro Thr Val Leu Gly Arg Leu Arg Glu Asp
180 185 190

Glu Gly Thr Trp Val Gln Val Ser Leu Leu His Phe Val Pro Thr Arg
195 200 205

Glu Ala Asn Gly His Arg Leu Gly Cys Gln Ala Ala Phe Pro Asn Thr
210 215 220

40 Thr Leu Gln Phe Glu Gly Tyr Ala Ser Leu Asp Val Lys Tyr Pro Pro
225 230 235 240

Val Ile Val Glu Met Asn Ser Ser Val Glu Ala Ile Glu Gly Ser His
245 250 255

45 Val Ser Leu Leu Cys Gly Ala Asp Ser Asn Pro Pro Pro Leu Leu Thr
260 265 270

Trp Met Arg Asp Gly Met Val Leu Arg Glu Ala Val Ala Glu Ser Leu
275 280 285

50 Tyr Leu Asp Leu Glu Glu Val Thr Pro Ala Glu Asp Gly Ile Tyr Ala
290 295 300

Cys Leu Ala Glu Asn Ala Tyr Gly Gln Asp Asn Arg Thr Val Glu Leu
305 310 315 320

55 Ser Val Met Tyr Ala Pro Trp Lys Pro Thr Val Asn Gly Thr Val Val

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	Glu Asp Asp Gly Glu Tyr Trp Cys Val Ala Glu Asn Gln Tyr Gly Gln 385 390 395 400		
15	Arg Ala Thr Ala Phe Asn Leu Ser Val Glu Phe Ala Pro Ile Ile Leu 405 410 415		
	Leu Glu Ser His Cys Ala Ala Ala Arg Asp Thr Val Gln Cys Leu Cys 420 425 430		
20	Val Val Lys Ser Asn Pro Glu Pro Ser Val Ala Phe Glu Leu Pro Ser 435 440 445		
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	Gln Ala Pro Pro Arg Val Ile Cys Thr Ser Arg Asn Leu Tyr Gly Thr 485 490 495		
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	Lys Ile Gly Pro Val Gly Ala Val Val Ala Phe Ala Ile Leu Ile Ala 515 520 525		
35	Ile Val Cys Tyr Ile Thr Gln Thr Arg Arg Lys Lys Asn Val Thr Glu 530 535 540		
	Ser Pro Ser Phe Ser Ala Gly Asp Asn Pro His Val Leu Tyr Ser Pro 545 550 555 560		
40	Glu Phe Arg Ile Ser Gly Ala Pro Asp Lys Tyr Glu Ser Glu Lys Arg 565 570 575		
	Leu Gly Ser Glu Arg Arg Leu Leu Gly Leu Arg Gly Glu Pro Pro Glu 580 585 590		
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<213> Rattus norvegicus

<220>
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5 Ser Ser Gly Phe Arg Ser Gln Ser Trp Ser Arg Gly Ser Pro Ser Thr
35 40 45

Val Ser Ser Ser Tyr Lys Arg Ser Ala Leu Ala Pro Arg Leu Ala Tyr
50 55 60

10 Ser Ser Ala Met Leu Ser Ser Ala Glu Ser Ser Leu Asp Phe Ser Gln
65 70 75 80

Ser Ser Ser Leu Leu Asn Gly Gly Ser Gly Gly Asp Tyr Lys Leu Ser
85 90 95

15 Arg Ser Asn Glu Lys Glu Gln Leu Gln Gly Leu Asn Asp Arg Phe Ala
100 105 110

Gly Tyr Ile Glu Lys Val His Tyr Leu Glu Gln Gln Asn Lys Glu Ile
115 120 125

20 Glu Ala Glu Ile His Ala Leu Arg Gln Lys Gln Ala Ser His Ala Gln
130 135 140

Leu Gly Asp Ala Tyr Asp Gln Glu Ile Arg Glu Leu Arg Ala Thr Leu
145 150 155 160

25 Glu Met Val Asn His Glu Lys Ala Gln Val Gln Leu Asp Ser Asp His
165 170 175

Leu Glu Glu Asp Ile His Arg Leu Lys Glu Arg Phe Glu Glu Glu Ala
180 185 190

30 Arg Leu Arg Asp Asp Thr Glu Ala Ala Ile Arg Ala Val Arg Lys Asp
195 200 205

Ile Glu Glu Ser Ser Met Val Lys Val Glu Leu Asp Lys Lys Val Gln
210 215 220

35 Ser Leu Gln Asp Glu Val Ala Phe Leu Arg Ser Asn His Glu Glu Glu
225 230 235 240

Val Ala Asp Leu Leu Ala Gln Ile Gln Ala Ser His Ile Thr Val Glu
245 250 255

40 Arg Lys Asp Tyr Leu Lys Thr Asp Ile Ser Thr Ala Leu Lys Glu Ile
260 265 270

Arg Ser Gln Leu Glu Cys His Ser Asp Gln Asn Met His Gln Ala Glu
275 280 285

Glu Trp Phe Lys Cys Arg Tyr Ala Lys Leu Thr Glu Ala Ala Glu Gln
290 295 300

50 Asn Lys Glu Ala Ile Arg Ser Ala Lys Glu Glu Ile Ala Glu Tyr Arg
305 310 315 320

Arg Gln Leu Gln Ser Lys Ser Ile Glu Leu Glu Ser Val Arg Gly Thr
325 330 335

55 Lys Glu Ser Leu Glu Arg Gln Leu Ser Asp Ile Glu Glu Arg His Asn

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5	His Asp Leu Ser Ser Tyr Gln Asp Thr Ile Gln Gln Leu Glu Asn Glu	355	360		365
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10	Asp Leu Leu Asn Val Lys Met Ala Leu Asp Ile Glu Ile Ala Ala Tyr	385	390	395	400
	Arg Lys Leu Leu Glu Gly Glu Glu Thr Arg Phe Ser Thr Phe Ser Gly	405	410		415
15	Ser Ile Thr Gly Pro Leu Tyr Thr His Arg Gln Pro Ser Val Thr Ile	420	425		430
	Ser Ser Lys Ile Gln Lys Thr Lys Val Glu Ala Pro Lys Leu Lys Val	435	440	445	
20	Gln His Lys Phe Val Glu Glu Ile Ile Glu Glu Thr Lys Val Glu Asp	450	455	460	
	Glu Lys Ser Glu Met Glu Asp Ala Leu Thr Val Ile Ala Glu Glu Leu	465	470	475	480
25	Ala Ala Ser Ala Lys Glu Glu Lys Glu Glu Ala Glu Glu Lys Glu Glu	485	490		495
	Glu Pro Glu Val Lys Ser Pro Val Lys Ser Pro Glu Ala Lys Glu Glu	500	505		510
30	Glu Glu Gly Glu Lys Glu Glu Glu Glu Glu Gly Gln Glu Glu Glu Glu	515	520	525	
	Glu Glu Asp Glu Gly Val Lys Ser Asp Gln Ala Glu Glu Gly Gly Ser	530	535	540	
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	Gly Glu Thr Glu Ala Glu Gly Glu Gly Glu Glu Ala Glu Ala Lys Glu	565	570		575
40	Glu Lys Lys Thr Glu Gly Lys Val Glu Glu Met Ala Ile Lys Glu Glu	580	585	590	
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45	Pro Val Glu Glu Val Lys Pro Lys Pro Glu Ala Lys Ala Gly Lys Asp	610	615	620	
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	Asp Val Pro Asp Lys Lys Lys Ala Glu Ser Pro Val Lys Glu Lys Ala	660	665		670
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Val Glu Glu Met Ile Thr Ile Thr Lys Ser Val Lys Val Ser Leu Glu
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5 Lys Asp Thr Lys Glu Glu Lys Pro Gln Gln Gln Glu Lys Val Lys Glu
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Lys Ala Glu Glu Glu Gly Gly Ser Glu Glu Glu Val Gly Asp Lys Ser
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10 Pro Gln Glu Ser Lys Lys Glu Asp Ile Ala Ile Asn Gly Glu Val Glu
725 730 735

Gly Lys Glu Glu Glu Glu Gln Glu Thr Gln Glu Lys Gly Ser Gly Gln
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15 Glu Glu Glu Lys Gly Val Val Thr Asn Gly Leu Asp Val Ser Pro Ala
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20 Lys Lys Val Glu Lys Ile Thr Ser Glu Gly Gly Asp Gly Ala Thr Lys
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Tyr Ile Thr Lys Ser Val Thr Val Thr Gln Lys Val Glu Glu His Glu
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 30 <213> Rattus norvegicus

<220>
 <223> Neurodegeneration associated protein 1

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 35 40 45
 Met Thr Arg His Glu Arg Ser Leu Gly Arg Ala Gly Asp Asp Tyr Glu
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 45 Val Leu Glu Leu Asp Asp Val Ala Lys Glu Asn Thr Ala Gly Ser Ser
 65 70 75 80
 Ser Leu Asp Gln Val His Pro Ser Leu Pro Ser Glu Thr Thr Val Glu
 85 90 95
 50 Lys Ser Glu Thr Glu Ile Pro Thr Cys Gly Pro Ala Leu Asn Gln Ser
 100 105 110
 Thr Glu Ser Asn Pro Ser Val Ala Thr Val Cys His Ser Glu Glu Val
 115 120 125

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10	Asn	Asp	Ser	Leu	Gln	Leu	Cys	Ala	Gln	Ala	Val	Glu	Gly	Gly	Arg	Arg	
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15	Glu	Arg	Tyr	Ala	Asp	Leu	Cys	Pro	Ser	Val	Pro	Ser	Leu	Ser	Gly	Glu	
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20	Ser	Ala	Gly	Asp	Ala	Glu	Ala	Val	His	Gln	Asp	Gly	Gln	Glu	Phe	Gln	
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				260					265					270			
25	Asp	Gln	Gly	Arg	Gln	Thr	Glu	Asn	Ser	Thr	Glu	Asp	Ala	Asp	Cys	Val	
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30	Ser	Ser	Pro	Glu	Gln	Val	Val	Arg	Pro	Lys	Val	Arg	Lys	Val	Ile	Ser	
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	Ser	Ser	Gln	Val	Asp	Gln	Glu	Ser	Gly	Phe	Asn	Arg	His	Glu	Ala	Lys	
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50	Tyr	Gln	Leu	Phe	Asp	Lys	Asp	Glu	Asp	Ser	Ser	Glu	Cys	Ser	Asp	Gly	
			420					425						430			
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55	Gln	Ser	Ser	Ser	Asp	Glu	Ser	Trp	Glu	Thr	Leu	Pro	Gly	Lys	Asp	Glu	
	450						455					460					

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 465 470 475 480
 Gln Glu Leu Ser Leu Gln Glu Gly Glu Gln Thr Ser Leu Glu Glu Gly
 485 490 495
 10 Glu Ile Pro Trp Leu Gln Tyr Asn Glu Val Asn Glu Ser Ser Ser Asp
 500 505 510
 Glu Gly Asn Glu Pro Ala Asn Glu Phe Ala Gln Pro Glu Ala Phe Met
 515 520 525
 15 Leu Asp Gly Asn Asn Asn Leu Glu Asp Asp Ser Ser Val Ser Glu Asp
 530 535 540
 Leu Asp Val Asp Trp Ser Leu Phe Asp Gly Phe Ala Asp Gly Leu Gly
 545 550 555 560
 20 Val Ala Glu Ala Ile Ser Tyr Val Asp Pro Gln Phe Leu Thr Tyr Met
 565 570 575
 Ala Leu Glu Glu Arg Leu Ala Gln Ala Met Glu Thr Ala Leu Ala His
 580 585 590
 25 Leu Glu Ser Leu Ala Val Asp Val Glu Val Ala Asn Pro Pro Ala Ser
 595 600 605
 Lys Glu Ser Ile Asp Gly Leu Pro Glu Thr Leu Val Leu Glu Asp His
 610 615 620
 30 Thr Ala Ile Gly Gln Glu Gln Cys Cys Pro Ile Cys Cys Ser Glu Tyr
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	Arg Asp Leu Thr Thr Ser Ser Val Glu Lys Asp Asn Gly Gly Lys Thr				
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	Ser Ala Pro Ser Gln Thr Asp Ser Asp Val Pro Pro Glu Thr Glu Glu	2050	2055	2060	
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Glu Arg Tyr His Ser Leu Ala Pro Met Tyr Tyr Arg Gly Ala Gln Ala
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Ala Ile Val Val Tyr Asp Ile Thr Asn Thr Asp Thr Phe Ala Arg Ala
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Lys Asn Trp Val Lys Glu Leu Gln Arg Gln Ala Ser Pro Asn Ile Val
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Ile Ala Leu Ala Gly Asn Lys Ala Asp Leu Ala Ser Lys Arg Ala Val
130 135 140
Glu Phe Gln Glu Ala Gln Ala Tyr Ala Asp Asp Asn Ser Leu Leu Phe
145 150 155 160
Met Glu Thr Ser Ala Lys Thr Ala Met Asn Val Asn Glu Ile Phe Met
165 170 175
Ala Ile Ala Lys Lys Leu Pro Lys Asn Glu Pro Gln Asn Ala Thr Gly
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Ala Pro Gly Arg Asn Arg Gly Val Asp Leu Gln Glu Asn Asn Pro Ala
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210

215

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<213> Homo sapiens

10
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<223> Rab5c-like protein

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gggaacaaga tctgtcaatt taagctgggt ctgctggggg agtctgcggt agggcaatcc 180
15 agcctcgtcc tccgctttgt caaggagacag ttacacgagt accaggagag cacaattgga 240
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gcagacctgg ccagcaagag agccgtggaa ttccaggaag cacaagccta tgcagacgac 540
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35 40 45
Thr Val Gln Leu Arg Asn Gly Asn Leu Gln Tyr Asp Leu His Tyr Trp
50 55 60
55 Leu Gly Asn Glu Cys Ser Gln Asp Glu Ser Gly Ala Ala Ala Ile Phe

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	Gly Leu Lys Tyr Lys	115	Lys Gly Gly Val Ala	120	Ser Gly Phe Lys His	125	Val
10	Val Pro Asn Glu Val	130	Val Val Val Gln Arg	135	Leu Phe Gln Val Lys	140	Gly Arg
	Arg Val Val Arg Ala	145	Thr Glu Val Pro Val	150	Ser Trp Asp Ser Phe	155	Asn
15	Asn Gly Asp Cys Phe	165	Ile Leu Asp Leu Gly	170	Asn Asn Ile Tyr Gln	175	Trp
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20	Ser Lys Gly Ile Arg	195	Asp Asn Glu Arg Ser	200	Gly Arg Ala Gln Val	205	His
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25	Pro Lys Pro Ala Leu	225	Pro Glu Gly Thr Glu	230	Asp Thr Ala Lys Glu	235	Asp
	Ala Ala Asn Arg Lys	245	Leu Ala Lys Leu Tyr	250	Lys Val Ser Asn Gly	255	Ala
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	Gly Pro Leu Arg Ser	275	Glu Asp Cys Phe Ile	280	Leu Asp His Gly Arg	285	Asp
35	Gly Lys Ile Phe Val	290	Trp Lys Gly Lys Gln	295	Ala Asn Met Glu Glu	300	Arg
	Lys Ala Ala Leu Lys	305	Thr Ala Ser Asp Phe	310	Ile Ser Lys Met Gln	315	Tyr
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45	Gly Pro Gly Leu Gly	355	Tyr Leu Ser Ser His	360	Ile Ala Asn Val Glu	365	Arg
50	Val Pro Phe Asp Ala	370	Gly Thr Leu His Thr	375	Ser Thr Ala Met Ala	380	Ala
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55							400

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15	Pro	Ala	His	Leu	Met	Ser	Leu	Phe	Gly	Gly	Lys	Pro	Met	Ile	Ile	Tyr	
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25	Leu	Lys	Thr	Pro	Ser	Ala	Ala	Tyr	Leu	Trp	Val	Gly	Ala	Gly	Ala	Ser	
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 <223> Gelsolin

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<220>
 <223> Cd81 antigen

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 10 Leu Gly Asp Lys Pro Ala Pro Ser Thr Phe Tyr Val Gly Ile Tyr Ile
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 15 Tyr Gly Ala Ile Gln Glu Ser Gln Cys Leu Leu Gly Thr Phe Phe Thr
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 Cys Leu Val Ile Leu Phe Ala Cys Glu Val Ala Ala Gly Ile Trp Gly
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 20 Phe Val Asn Lys Asp Gln Ile Ala Lys Asp Val Lys Gln Phe Tyr Asp
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 145 150 155 160
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 165 170 175
 30 Ser Ser Ser Asn Ser Phe Thr Gln Leu Leu Lys Glu Asp Cys His Gln
 180 185 190
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 35 40 45
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 35 Cys Gln Lys Thr Arg Leu Arg Arg Arg Ser Arg Ser Thr Pro Arg Lys
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 45 <213> Rattus norvegicus

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 55 ccagaagacc agattgagaa ggaggagcag gtcaacccca agaaaaaagt gaccgagaag 360
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 35 <212> PRT
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<220>
 <223> Syntaxin binding protein 2

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 35 40 45
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 50 50 55 60
 Arg Glu Pro Ile Pro Ser Leu Glu Ala Ile Tyr Leu Leu Ser Pro Thr
 65 70 75 80
 55 Glu Lys Ala Leu Ile Lys Asp Phe Gln Gly Thr Pro Thr Phe Thr Tyr
 85 90 95

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 115 120 125
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 10 Asp Ala Pro His Ser Thr Tyr Asn Leu Tyr Cys Pro Phe Arg Ala Glu
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 15 Cys Ala Thr Leu Gln Glu Tyr Pro Ala Ile Arg Tyr Arg Lys Gly Pro
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 20 Phe Lys Ala Asp Thr Pro Ser Leu Gly Glu Gly Pro Glu Lys Thr Arg
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 Ser Gln Leu Leu Ile Met Asp Arg Ala Ala Asp Pro Val Ser Pro Leu
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 Glu Gln Asp Thr Tyr Arg Tyr Glu Thr Thr Gly Leu Ser Glu Ala Arg
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 30 Glu Lys Ala Val Leu Leu Asp Glu Asp Asp Asp Leu Trp Val Glu Leu
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355

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<213> Rattus norvegicus

<220>
<223> Schwann cell peripheral myelin

<400> 111

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 <213> Rattus norvegicus

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 35 40 45
 Val Tyr Tyr Asn Glu Ala Thr Gly Gly Lys Tyr Val Pro Arg Ala Ile
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 Phe Gly Gln Ile Phe Arg Pro Asp Asn Phe Val Phe Gly Gln Ser Gly
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 Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
 100 105 110
 Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Ala Glu Ser Cys Asp
 115 120 125
 Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
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 Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Ile Arg Glu Glu Tyr Pro
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 Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
 165 170 175
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 Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
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 Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Cys Leu
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 Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
 245 250 255

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Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
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5 Leu Thr Ser Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
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Leu Thr Gln Gln Val Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
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10 Pro Arg His Gly Arg Tyr Leu Thr Val Ala Ala Val Phe Arg Gly Arg
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Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ala Val Thr Phe Ile
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Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys
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65 70 75 80
Glu Ala Thr Leu Thr Leu Val Asp Thr Gly Ile Gly Met Thr Lys Ala
85 90 95
Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala
100 105 110
Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile Ser Met Ile Gly Gln
115 120 125
Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Glu Lys Val Val
130 135 140

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 20 580 585 590
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 25 610 615 620
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25	Lys	Leu	Thr	Glu	Phe	Glu	Glu	Ala	Ile	Gly	Val	Ile	Phe	Thr	His	Val
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 caatgcctaa tgcatttgga caagttgata ggataactt tccaagatcg ttgtctgttg 180
 cagctggcca tgactcatcc aagtcacatc ttaaattttg gaatgaatcc tgatcatgcc 240
 aggaattcat tatctaactg tggaaattcgg cagcccaaat acggagacag aaaagttcat 300
 cacatgcaca tgcggaagaa agggattaac accttgataa atatcatgtc acgccttggc 360
 caagatgacc caactccctc gaggattaac cacaatgaac gggtggaatt cctgggtgat 420
 gctgttgttg aatttctgac cagcgtccat ttgtactatt tgtttcctag tctggaagaa 480
 ggaggattag caacctatcg gactgccatt gttcagaatc agcaccttgc catgctagca 540
 aagaaacttg aactggatcg atttatgctg tatgctcacg ggcctgacct ttgtagagaa 600
 tcggaccctc gacatgcaat ggccaattgt tttgaagcgt taataggagc tgtttacttg 660
 gagggaagcc tggaggaagc caagcagtta tttggacgct tgctctttaa tgatccggac 720
 ctgcgcaag tctggctcaa ttatcctctc caccactcc aactacaaga gccaaatact 780
 gatcgacaac ttattgaaac ttctccggtt ctacaaaaac ttactgagtt tgaagaagca 840
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 ggatttaacc atctgaccct aggccacaat cagagaatgg aattcctagg tgactccata 960
 atgcaactgg tagccacaga gtacttattc attcatttcc cagatcatca tgaaggacac 1020
 ttaactttgt tgcgaagctc tttggtgaat aatagaactc agggcaagggt agcggaggag 1080
 ctgggcatgc aggagtacgc cataaccaac gacaagacca agaggcctgt ggcgcttcgc 1140
 accaagacct tggcggacct tttggaatca tttattgcag cgctgtacat tgataaggat 1200
 ttggaatatg ttcatacttt catgaatgtc tgcttctttc cacgattgaa agagttcatt 1260
 ttgaatcagg attggaatga ccccaaatcc cagcttcagc agtggtgctt gacacttagg 1320
 acagaaggaa aagagccaga cattcctctg tacaagactc tgcagacagt gggcccatcc 1380
 catgcccga cctacactgt ggctgtttat ttcaagggag aaagaatagg ctgtgggaaa 1440
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 tttcccaga tggcccatca gaagcgggtc atcgaacgga agtacagaca agagttaaaa 1560
 gaaatgaggt gggaaaagaga gcatcaagag agagagccag atgagactga agacatcaag 1620
 aaataa 1626

Claims

1. Use of:

- (a) an isolated gene sequence that is down-regulated in the spinal cord of a mammal in response to mechanistically distinct first and second models of neuropathic or central sensitization pain;
- (b) an isolated gene sequence comprising a nucleic acid sequence of any of Tables I to VI;
- (c) an isolated gene sequence having at least 80% sequence identity with a nucleic acid sequence of any of Tables I to VI;
- (d) an isolated nucleic acid sequence that is hybridizable to any of the gene sequences according to (a), (b) or (c) under stringent hybridisation conditions;
- (e) a recombinant vector comprising a gene sequence or nucleic acid sequence according to any one of (a) to (d);
- (f) a host cell containing the vector according to (e);
- (g) a non-human animal having in its genome an introduced gene sequence or nucleic acid sequence or a removed or down-regulated gene sequence or nucleic acid sequence according to any one of (a) to (d);
- (h) an isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence according to any one of (a) to (d), or a polypeptide variant thereof

with sequential amino acid deletions from the C terminus and/or the N-terminus;
 (i) an isolated polypeptide encoded by a nucleotide sequence according to any one of (a) to (d); or
 (j) an isolated antibody that binds specifically to a polypeptide according to (h) or (i);

in the screening of compounds for the treatment of pain, or for the diagnosis of pain.

2. Use according to claim 1, wherein the isolated gene sequence is down-regulated both in response to streptozocin-induced diabetes and in response to surgical injury of a nerve leading to the spine.

3. Use according to claim 1 or 2 wherein the isolated gene sequence encodes a kinase.

4. Use according to claim 1, 2 or 3, wherein the isolated gene sequence encodes an expression product or fragment thereof of pyruvate kinase, M1 and M2 subunits (M24359; X97047; X56494).

5. Use according to claim 1 or 2, wherein the isolated gene sequence encodes an expression product or fragment thereof of a receptor.

6. Use according to claim 1, 2 or 5, wherein the isolated gene sequence encodes dopamine receptor D.sub.1 (I58000).

7. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a transporter.

8. Use according to claim 1, 2 or 7, wherein the isolated gene sequence encodes differentiation-associated Na⁺-dependent inorganic phosphate cotransporter (AF271235) or putative vacuolar assembly protein VSP41 gene (U87309).

9. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a G-protein coupled receptor protein.

10. Use according to claim 1, 2 or 9, wherein the isolated gene sequence encodes Glt1 (G-protein-coupled receptor kinase-interactor 1; GPCR kinase-associated ADP-ribosylation factor) (AF085693).

11. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a DNA-binding protein.

12. Use according to claim 1, 2 or 11, wherein the isolated gene sequence encodes putative histone H3.3A (X91866; M11354).

13. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a ligase.

14. Use according to claim 1, 2 or 13, wherein the isolated gene sequence encodes 3-Hydroxy 3-methylglutaryl coenzyme A synthase, cytosolic (X52625), acyl-CoA synthetase II, brain (D360666) farnesyl diphosphate synthase (M34477), bendless protein (AB032739; E12457), fatty acid synthase (X62888), glutamine synthetase (EC 6.3.1.2) (M91652), or putative seryl-tRNA synthetase (X91257).

15. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a lyase.

16. Use according to claim 1, 2 or 15, wherein the lyase is enolase, alpha alpha, non-neuronal (NNE) (X02610; X52379; M14328).

17. Use according to claim 1 or 2, wherein the isolated gene sequence encodes an oxidoreductase.

18. Use according to claim 1, 2 or 17, wherein the isolated gene sequence encodes aldose reductase, lens (AREC 11.1.21) (X05884) cytochrome-c oxidase I, mitochondrial (S79304), lactate dehydrogenase-B (LDH-B) (U07181; X51905; Y00711), putative cytochrome c oxidase VIB (EC 1.9.3.1) (X13923), putative NADH: ubiquinone oxidoreductase PGIV subunit (AF044953), putative succinate dehydrogenase flavoprotein (AF095938; AF171022), putative ubiquinol-cytochrome-c reductase (EC 1.10.2.2) core protein II (J04973) or stearoyl-coA desaturase 2 (AB032243; M26270).

19. Use according to claim 1 or 2, wherein the isolated sequence encodes a transferase.

20. Use according to claim 1, 2 or 19, wherein the isolated sequence encodes ribophorin I (X05300) or sulfotransferase-like protein (AF188699).

21. Use according to claim 1 or 2, wherein the isolated sequence encodes a hydrolase.

22. Use according to claim 1, 2 or 21, wherein the isolated sequence encodes ATP synthase, H⁺, alpha subunit, mitochondrial (EC 3.6.1.34) (X56133), F1F0 ATPase delta subunit (U00926), putative dihydropyrimidinase related protein (D78013), heat shock protein 90 (S45392; M18186; M16660), or putative ribonuclease III (AF116910).

23. Use according to claim 1 or 2, wherein the isolated sequence encodes myelin basic protein S (MBP S) (K00512), transferring (D38380), neurofilament, light molecular weight (NF-L) (AF031880), myelin-associated glycoprotein (MAG) (M16800; M31811), NF-M middle molecular weight neurofilament protein (M18628) neuro-degeneration associated- protein 1 (D32249), S-100 protein β -subunit (X01090), microtubule-associated protein 1b (Map 1b) (X60370; L06237), putative cdc 37 homolog (D26564), putative ras-related protein Rab-5c (U11293), putative gelsolin (J04953), Cd81 antigen (target of antiproliferative antibody 1) (U19894; X59047; M33680), Mobp81 (Myelin-associated/Oligo-dendrocytic basic protein 81) (X87900), syntaxin binding protein n-secl, sec1 homolog, A-internexin (M73049), putative β -sarcoglycan A3b (AB024921), CGI-78 protein (AF151835), KIAA0143 (D63477), septin 2 (D50918), Nucleobindin (Z36277), myelin protein SR13 (M69139; S55427), B-Actin, cytoplasmic (V01217; X03672), Iy6/neurotoxin (Lynx1) homolog (AD141377), astrocytic phosphoprotein ; PFA 15 gene (AJ243949; X86694), PLIC-1 (AF177345), Nfx1 (tip associating protein (TAP) gene) (AF093139; AF093140), A-Crystallin B (U04320; M73741 ; M28638), heat shock-like protein 70 kD (X70065; U73744; Y00371), tau microtubule-associated protein (X79321), myelin, Schwann cell, Perioheral (P-O) (K03242), B-Tubulin class 1 (AB011679; X04663; AF14139), putative long-chain polyunsaturated fatty acid elongation enzyme (Helo1) or peptidylglycine alpha-amidating monooxygenase 1.

24. A non-human animal having in its genome an introduced gene sequence or a removed or down-regulated gene sequence, said sequence being down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

25. A non-human animal according to claim 24, wherein said gene sequence becomes down regulated both in response to streptozocin induced diabetes and in response to chronic constriction injury.

26. A non-human animal according to claim 24 or 25, wherein the introduced gene sequence is according to any of claims 1 to 23.

27. A non-human animal according to any one of claims 24 to 26 which is *C. elegans*.

28. A kit comprising:

(a) affinity peptide and/or ligand and/or substrate for an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to a mechanistically distinct first and second models of neuropathic or central sensitization pain ; and

(b) a defined quantity of an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal both in response to first and second models of neuropathic or central sensitization pain, for simultaneous, separate or sequential use in detecting and/or quantifying down-regulation of a gene sequence in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

29. A kit according to claim 28, wherein the gene sequence is defined in any one of claims 1 to 23.

30. A kit comprising:

(a) nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain; and
(b) a defined quantity of one or more nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain,

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for simultaneous, separate or sequential use in detecting and/or quantifying down-regulation of a gene sequence in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

- 5 **31.** The kit of claim 30, wherein the gene sequence is according to any of claims 1 to 23.
- 32.** A compound that modulates the action of an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.
- 10 **33.** A compound according to claim 32 wherein the gene sequence is listed in Tables I to VI.
- 34.** A compound according to claim 32 or 33 wherein the nucleotide sequence is according to any one of claims 1 to 23.
- 35.** A compound according to any one of claims 32 to 34 for use as a medicament.
- 15 **36.** A compound according to any one of claims 32 to 35 for the treatment or diagnosis of pain.
- 37.** A pharmaceutical composition comprising a compound according to any one of claims 32 to 36 and a pharmaceutically acceptable carrier or diluent.
- 20 **38.** Use of a compound according to any one of claims 32 to 36 in the manufacture of a medicament for the treatment or diagnosis of pain.
- 39.** Use of a compound according to any one of claims 32 to 36 in the manufacture of a medicament for the treatment or diagnosis of chronic pain.
- 25 **40.** A method of treatment of pain, which comprises administering to a patient an effective amount of a compound according to any one of claims 32 to 36.



(12) **EUROPEAN PATENT APPLICATION**

(88) Date of publication A3:
26.05.2004 Bulletin 2004/22

(51) Int Cl.7: **C12Q 1/68, C07K 14/47,**
C12N 5/10, C12N 15/85

(43) Date of publication A2:
19.02.2003 Bulletin 2003/08

(21) Application number: **02255229.3**

(22) Date of filing: **26.07.2002**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
IE IT LI LU MC NL PT SE SK TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **27.07.2001 GB 0118354**
07.02.2002 GB 0202883

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(54) **Identification and use of molecules implicated in pain**

(57) The invention relates to the use of:

- (a) an isolated gene sequence that is down-regulated in the spinal cord of a mammal in response to mechanistically distinct first and second models of neuropathic or central sensitization pain;
- (b) an isolated gene sequence comprising a nucleic acid sequence of any of Tables I to VI;
- (c) an isolated gene sequence having at least 80% sequence identity with a nucleic acid sequence of any of Tables I to VI;
- (d) an isolated nucleic acid sequence that is hybridizable to any of the gene sequences according to (a), (b) or (c) under stringent hybridisation conditions;
- (e) a recombinant vector comprising a gene sequence or nucleic acid sequence according to any one of (a) to (d);
- (f) a host cell containing the vector according to (e);
- (g) a non-human animal having in its genome an introduced gene sequence or nucleic acid sequence or a removed or down-regulated gene sequence or nucleic acid sequence according to any one of (a) to (d);
- (h) an isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence ac-

cording to any one of (a) to (d), or a variant polypeptide thereof with sequential amino acid deletions from the C terminus and/or the N-terminus;
(i) an isolated polypeptide encoded by a nucleotide sequence according to any one of (a) to (d); or
(j) an isolated antibody that binds specifically to a polypeptide according to (h) or (i);

in the screening of compounds for the treatment of pain, or for the diagnosis of pain.

The invention also relates to the use of naturally occurring compounds such as peptide ligands of the expression products of the above gene sequences and their associated signal transduction pathways for use in the treatment of pain.



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which under Rule 45 of the European Patent Convention EP 02 25 5229 shall be considered, for the purposes of subsequent proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (InI.CI.7)
X	SHAH B ET AL: "Beta3, An auxiliary subunit of the voltage gated sodium channel is upr" SOCIETY FOR NEUROSCIENCE ABSTRACTS, SOCIETY FOR NEUROSCIENCE, US, vol. 26, no. 1-2, 4 November 2000 (2000-11-04), page 938, ABSTRACTN03526, XP009020087 ISSN: 0190-5295 * the whole document *	1-3, 24-31	C12Q1/68 C07K14/47 C12N5/10 C12N15/85
Y	BITAR MILAD S ET AL: "Attenuation of IGF-1 antinociceptive action and a reduction in spinal cord gene expression of its receptor in experimental diabetes" PAIN, vol. 75, no. 1, March 1998 (1998-03), pages 69-74, XP002262337 ISSN: 0304-3959 * the whole document *	1-3, 24-31	
			TECHNICAL FIELDS SEARCHED (InI.CI.7)
			C12Q C07K C12N
INCOMPLETE SEARCH The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims. Claims searched completely : Claims searched incompletely : Claims not searched : Reason for the limitation of the search: see sheet C			
Place of search		Date of completion of the search	Examiner
Munich		3 December 2003	Hermann, P
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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INCOMPLETE SEARCH
SHEET C

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The following comments apply to the invention for which a search has been performed - i.e. claims 1, 2, 24-40 (in part) and 3-4 (in full) relating to the first invention of the application.

The applicant should therefore bear in mind that, should he pay additional search fees, further objections leading to incomplete search might as well arise during the search phase of the further inventions.

Claim(s) searched completely:
2-4, 26

Claim(s) searched incompletely:
1, 24, 25, 27-31

Claim(s) not searched:
32-40

Reason for the limitation of the search:

a) Article 52 (4) EPC - Method for treatment of the human or animal body by therapy (claim 40).

Although claim 40 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search could have been carried out and based on the alleged effects of the compound/composition. However, in view of the lack of clarity of said claim (see item (f) hereinbelow) no search has been carried out.

b) The isolated gene sequence of part (a) of claim 1 is only defined by a result achieved in special conditions, and the description is silent as to any other characteristic features pertaining to said isolated gene sequence. Claim 1 therefore lacks clarity (Article 84 EPC), and could only be searched as it relates to the isolated gene sequences of table I encoding a kinase, and derivative thereof as listed in parts (c)-(j) of claim 1, all relating to kinase encoding nucleic acid sequences.

c) The non-human animal of present claims 24 or 25 or the *C. elegans* of claim 27 is defined by reference to the following parameter:

- the modification of the presence or expression of a gene sequence which is downregulated in the spinal cord of a mammal in response to two models of neuropathic pain and claim 25, as for it, limits those two models to the streptozocin induced-diabetes and the chronic constriction injury.

The use of that parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC (see also Guidelines C-III, 4.7a). For the same reasons as those hereinabove under item (b), the search for claims 24, 25 and 27 has been restricted to



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non-human animal wherein the introduced gene sequence is one of the sequences listed in Table I, encoding a kinase.

d) The expression product of a gene sequence and the nucleic acid sequence of the kits of claims 28-31 are only defined by a parameter - i.e. the expression product of said gene sequence or the nucleic acid sequence that is downregulated in the spinal cord of a mammal in response to two models of neuropathic pain. The use of that parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC (see also Guidelines C-III, 4.7a). For the same reasons as those hereinabove under item (b), the search for claims 28-31 has been restricted respectively to the product of the gene sequences given in Table I and to the sequences given in Table I themselves.

e) Moreover in independent claim 28 none of the characteristic features of the "affinity peptide", "ligand" and "substrate" for the expression product are given in said claim, and the description is also silent as to said eventual characteristics. Therefore the skilled person would not clearly understand which compounds are falling under the scope of said claim. Said claim therefore lacks clarity (Article 84 EPC) to such an extent that a meaningful search on its entire scope could not be performed. Said search has been restricted to substrates known for the kinases encoded by the gene sequences listed in table I.

f) Claims 32-36 relate to compounds only defined by the result to be achieved and the claims as well as the description do not relate to any features which would allow the skilled person to clearly understand which compounds are falling under the scope of said claims. Said claims therefore lack clarity (Article 84 EPC) to such an extent that no meaningful search could be performed.

As claims 37-40 are depending upon one or more of claims 32-36, said claims therefore lack clarity (Article 84 EPC) and could not be searched either.



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PARTIAL EUROPEAN SEARCH REPORT

Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	BLACKBURN-MUNRO G ET AL: "The sodium channel auxiliary subunits beta1 and beta2 are differentially expressed in the spinal cord of neuropathic rats" NEUROSCIENCE, vol. 90, no. 1, April 1999 (1999-04), pages 153-164, XP002262713 ISSN: 0306-4522 * the whole document *	1-3, 24-31	
A	NAKAMURA JIRO ET AL: "A protein kinase C-beta-selective inhibitor ameliorates neural dysfunction in streptozotocin-induced diabetic rats" DIABETES, vol. 48, no. 10, October 1999 (1999-10), pages 2090-2095, XP002260473 ISSN: 0012-1797 * the whole document *	1-3, 24-31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	LUO Z DAVID ET AL: "Neuronal nitric oxide synthase mRNA upregulation in rat sensory neurons after spinal nerve ligation: Lack of a role in allodynia development" JOURNAL OF NEUROSCIENCE, vol. 19, no. 21, 1 November 1999 (1999-11-01), pages 9201-9208, XP002262714 ISSN: 0270-6474 * the whole document *	1-3, 24-31	
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EPO FORM 1503 03.82 (P04C10)



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Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	FOX ALYSON ET AL: "Critical evaluation of the streptozotocin model of painful diabetic neuropathy in the rat" PAIN, vol. 81, no. 3, June 1999 (1999-06), pages 307-316, XP002260439 ISSN: 0304-3959 * the whole document *	1-3, 24-31	
A	COURTEIX C ET AL: "Streptozocin-induced diabetic rats: Behavioural evidence for a model of chronic pain" PAIN, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 53, no. 1, 1993, pages 81-88, XP009020332 ISSN: 0304-3959 * the whole document *	1-3, 24-31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	MALMBERG ANNIKA B ET AL: "Preserved acute pain and reduced neuropathic pain in mice lacking PKC-gamma" SCIENCE (WASHINGTON D C), vol. 278, no. 5336, 1997, pages 279-283, XP002260438 ISSN: 0036-8075 * the whole document *	1-3, 24-31	
A	WO 00/63427 A (CUVILLIER GWLADYS ;DEVGEN NV (BE); BOGAERT THIERRY (BE); PLATTEEUW) 26 October 2000 (2000-10-26) * the whole document *	1-3, 24-31	
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Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	TAO Y -X ET AL: "Expression and action of cyclic GMP-dependent protein kinase Ialpha in inflammatory hyperalgesia in rat spinal cord" NEUROSCIENCE, vol. 95, no. 2, 1 December 2000 (2000-12-01), pages 525-533, XP002260437 ISSN: 0306-4522 * the whole document *	1-3, 24-31	
A	BRIDGES D ET AL: "MECHANISMS OF NEUROPATHIC PAIN" BRITISH JOURNAL OF ANAESTHESIA, BJM PUBLISHING GROUP, LONDON, GB, vol. 87, no. 1, 2001, pages 12-26, XP001068882 ISSN: 0007-0912 * the whole document *	1-3, 24-31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
T	CIRUELA A ET AL: "Identification of MEK1 as a novel target for the treatment of neuropathic pain." BRITISH JOURNAL OF PHARMACOLOGY, vol. 138, no. 5, March 2003 (2003-03), pages 751-756, XP002260445 ISSN: 0007-1188 (ISSN print) * the whole document *	1-3, 24-31	

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:
- 1, 2, 24-40 (in part) 3-4 (in full)



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Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Invention 1: 1, 2, 24-40 (in part) 3-4 (in full)

Invention 1 relates to: i) the use of an isolated gene sequence encoding a kinase according to Table I, or derivative thereof such as recombinant vector, host cells or non-human animal comprising said isolated gene sequence, or isolated polypeptide encoded by, or comprising an isolated polypeptide encoded by said isolated gene sequence or isolated antibody directed against the above cited polypeptides, in the screening of compounds for the treatment of pain, or for the diagnosis of pain; ii) a non-human animal having introduced in its genome, said isolated gene sequence; iii) kits comprising either the expression product of said isolated gene sequence and its substrate, ligand or affinity peptide; iv) a compound that modulates the action of the expression product of said selected gene sequence; v) a pharmaceutical composition comprising said compound; vi) the use of said compound for the treatment or the diagnosis of pain; and vii) a method of treatment of pain which comprises administering to a patient an effective amount of said compound.

Invention 2: 1, 2, 24-40 (in part) 5-6 (in full)

Invention 2 is equivalent to invention 1 for an isolated gene sequence encoding an expression product or a fragment thereof of a receptor according to Table II.

Invention 3: 1, 2, 24-40 (in part) 7-8 (in full)

Invention 3 is equivalent to invention 1 for an isolated gene sequence encoding a transporter according to Table III.

Invention 4: 1, 2, 24-40 (in part) 9-10 (in full)

Invention 4 is equivalent to invention 1 for an isolated gene sequence encoding a G-protein coupled receptor protein according to Table IV.

Invention 5: 1, 2, 24-40 (in part) 11-12 (in full)

Invention 5 is equivalent to invention 1 for an isolated gene sequence encoding a DNA-binding protein according to Table V.

Invention 6: 1, 2, 24-40 (in part) 13-14 (in full)



European Patent
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LACK OF UNITY OF INVENTION
SHEET B

Application Number
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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Invention 6 is equivalent to invention 1 for an isolated gene sequence encoding a ligase according to rows 1-7 of Table VI.

Invention 7: 1, 2, 24-40 (in part) 15-16 (in full)

Invention 7 is equivalent to invention 1 for an isolated gene sequence encoding a lyase according to row 8 of Table VI.

Invention 8: 1, 2, 24-40 (in part) 17-18 (in full)

Invention 8 is equivalent to invention 1 for an isolated gene sequence encoding an oxido-reductase according to rows 9-16 of Table VI.

Invention 9: 1, 2, 24-40 (in part) 19-20 (in full)

Invention 9 is equivalent to invention 1 for an isolated gene sequence encoding a transferase according to rows 17-18 of Table VI.

Invention 10: 1, 2, 24-40 (in part) 21-22 (in full)

Invention 10 is equivalent to invention 1 for an isolated gene sequence encoding a hydrolase according to rows 19-21 and 54 of Table VI.

Invention 11: 1, 2, 23-40 (in part)

Invention 11 is equivalent to invention 1 for an isolated gene sequence encoding a protein according to 23rd row of Table VI.

Inventions 12-41: 1, 2, 23-40 (in part)

Inventions 12-41 are equivalent to invention 1 for an isolated gene sequences encoding a protein according to the 24th-53rd rows of Table VI respectively.

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 02 25 5229

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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